IN THE SUPREME COURT OF INDIA

CIVIL ORIGINAL JURISDICTION

WRIT PETITION (CIVIL) NO. 607 of 2021

IN THE MATTER OF:

DR. JACOB PULIYEL …PETITIONER

VERSUS

UNION OF INDIA & ORS. …RESPONDENTS

COUNTER AFFIDAVIT ON BEHALF OF THE RESPONDENT NO. 1 (MINISTRY OF HEALTH AND FAMILY WELFARE) AND RESPONDENT NO 2. (CENTRAL DRUGS STANDARD CONTROL ORGANISATION)

PAPER-BOOK

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ADVOCATE FOR RESPONDENT 1 & 2: G S MAKKER

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I, Dr. P.B.N. Prasad, S/o Sh. P. Somaiah Naidu, aged about 58 years, working as Joint Drugs Controller (India), Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, do hereby solemnly affirm and state as under, on the basis of information provided to me through official records:

1. That I am working as Joint Drugs Controller (India), Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. It is submitted that, I am

authorized to represent the Respondents in the above matter and as such I am well conversant with the facts and circumstances of the case on the basis of documents. Hence, I am competent to swear this affidavit.

2. That, I have gone through the contents of the writ petition filed by the Petitioner and I have perused the records pertaining to the case and I am filing this affidavit in reply, on the basis of knowledge derived by me after perusing the records.

3. It is submitted that the Answering Respondents deny and dispute all allegations and contentions raised by the Petitioner in the writ petition. The Answering Respondents humbly submit that the contents of the writ petition are denied, except to the extent admitted below and nothing shall be deemed to have been admitted by the Answering Respondents merely on the ground of non-specific traverse.

4. At the outset, the Respondents seek to raise the following preliminary objections-

(a) It is submitted that this petition is filed purportedly as a Public Interest Litigation. There are very few cases where a purported Public Interest Litigation [whether bonafide or motivated] harms public interest directly. This is

one such petition which, if entertained, would harm public interest.

(b) It is submitted that the year 2020 and 2021 witnessed one of the most severe tragedy engulfing not only India but entire human kind, threatening virtually the existence of the human race. It has posed unprecedented challenges before the human race. Every country started their own earnest efforts to deal with this pandemic called COVID-19. All human efforts throughout the world were concentrated towards tackling this pandemic and also attempting to prevent it.

(c) It was only few countries in the world which succeeded in manufacturing vaccines for protection from Covid-19. India is one of such countries which succeeded in developing its own vaccine and also manufacturing one more vaccine invented in Britain, known respectively as Covaxin and Covishield. As narrated hereunder in detail, there is an elaborate statutory regime which needs to be followed before any vaccination drive starts. India, as a nation, has a statutory regime in place and the

said regime is followed scrupulously as pointed out hereunder in detail.

(d) The Petitioner was a member of a group of experts called National Technical Advisory Group on Immunisation ("**NTAGI**") which group consists of qualified epidemiologists, infectious disease experts and clinical trialists and others and is, therefore, fully aware of the protocol in the form of a statutory regime.

(e) The country started one of the largest vaccination preparations in the world with most adverse circumstances, like different educational levels of the citizens, the effect of pandemic at its peak which posed its own challenges in vaccination etc. and initial vaccine hesitancy. The vaccines which have undergone the statutory regime and are safe were required to be administered to each and every individual in the country not only in his / her interest but also in larger public interest.

(f) The Government of India and Governments of the States, therefore, started a massive drive to inform and educate people to get themselves vaccinated. This largest vaccination drive in the world successfully gained momentum with joint

efforts of all in one and more than hundreds of crores of vaccinations have already been administered.

(g) Any misgivings and misconceived doubts and motivated propaganda against vaccination can only result into a potential threat of setting vaccine hesitancy again, which will not be in public interest. Once it is placed before this Hon'ble Court that –

(i) there is a statutory regime in place; and

(ii) the regime is followed;

this Hon'ble Court, may not undertake the exercise any further as it would enable the petitioner and handful of others like him to create serious misgivings and misconceived doubts against the vaccination in the process of this petition itself.

5. At this juncture, the entire concentration of the Central Government and the State Governments should be and is on vaccination drive and encouraging people to get them vaccinated. It is, therefore, not desirable at this juncture to invest time finding out motives behind few elements attempting to act against the interest of nation at

the cost of violating the right of crores of citizens to be protected from pandemic.

6. At the further outset, it is respectfully submitted that the subject matter of the present petition is vaccination at a crucial juncture, when a sudden pandemic has engulfed the world. Once it is pointed out that a statutory regime exists for certification and permission to administer any drug / vaccine, this Hon'ble Court would not exercise its power of judicial review for the purpose of taking any other possible view as such examination would be out of the scope of the judicial review. The petitioner cannot, under the garb of a petition under Article 32 of the Constitution, pray before this Hon'ble Court to sit in appeal over a scientific process undertaken by the domain experts and take a different view on a subject which is not the subject of expertise of any judicial forum.

7. The Petitioner is fully aware of the facts narrated hereunder. He has chosen to give a false picture before this Hon'ble Court for the reasons best known to him. In the process, however, he has raised a false alarm and warning against efforts of the nation to combat an unprecedented tragedy faced by human race. Such an attempt is to be viewed very seriously at a time when the Central Government, all State Governments and Union Territories are individually and collectively making all possible efforts

to vaccinate every individual. This Hon'ble Court may, therefore, be pleased to dismiss this petition as not maintainable, hit by principles of suppression of material facts and the subject matter being outside the scope of judicial review with exemplary costs.

8. It is submitted that, the Petitioner has approached this Hon'ble Court seeking the following reliefs, *inter alia*:-

> "*…a) Direct the respondents to release the entire segregated trial data for each of the phases of trials that have been undertaken with respect to the vaccines being administered in India; and*
>
> *…b) Direct the respondent no.2 to disclose the detailed minutes of the meetings of the Subject Expert Committee and the NTGAI with regard to the vaccines as directed by the 59th Parliamentary Standing Committee Report and the members who constituted the committee for the purpose of each approval meeting; and*
>
> *…c) Direct the respondent no.2 to disclose the reasoned decision of the DCGI granting approval or rejecting an application for emergency use authorization of vaccines and the documents and reports submitted to the DCGI in support of such application; and*
>
> *…d) Direct the respondents to disclose the post vaccination data regarding adverse events, vaccinees who got infected with Covid, those who needed hospitalization and those who died after such infection post vaccination and direct the respondents to widely publicize the data collection of such adverse event*

through the advertisement of toll free telephone numbers where such complains can be registered; and

…e) Declare that vaccine mandates, in any manner whatsoever, even by way of making it a precondition for accessing any benefits or services, is a violation of rights of citizens and unconstitutional; and

…f) Pass any other orders as this Hon'ble Court deems fit…"

9. It is submitted that, the Drugs and Cosmetics Act 1940 is a central legislation, that regulates the import, manufacture, distribution and sale of drugs and cosmetics in the country. The main objective of the Drugs and Cosmetics Act, 1940 is to ensure that the drugs available to the people are safe and efficacious and conform to prescribed quality standards and that the cosmetics marketed are safe for use.

10. The Ministry of Health and Family Welfare has made New Drugs and Clinical Trials Rules, 2019 (hereafter as "***Rules of 2019***") published in G.S.R.227 (E) dated 19.03.2019 under the Drugs and Cosmetics Act, 1940. It is submitted that, the Rules of 2019 came into effect from 19.03.2019 and substituted relevant parts of the Drugs and Cosmetics Rules, 1945.

A True copy of the New Drugs and Clinical Trials Rules, 2019 is annexed herewith and marked as **ANNEXURE R/1** at pg. **59-176.**

11. It is submitted that, as per the statutory regime contained in the provisions of the Rules of 2019, clinical trials and permission to import or manufacture New Drugs including Vaccines are granted by Central Licensing Authority i.e. Drugs Controller General ("**CDSCO**").

12. Under the Rules of 2019, the first, second and third schedule have details regarding "*general principles and practices for clinical trial*", "*requirements and guidelines for permission to import or manufacture of new drug for sale or to undertake clinical trial*" and "*conduct of clinical trial*" respectively.

13. For the present purpose, the Second Schedule to the Rules of 2019 are relevant, which as stated above, provides the requirements and guidelines for permission to import and / or manufacture new drugs for sale or to undertake clinical trials in the country.

14. Under the Second Schedule, an applicant is required to make an application for grant of permission to import and / or manufacture new drugs for sale or to undertake clinical trials (in the present case for Covid-19 vaccines) accompanied with data in accordance with the Rules of 2019. This data includes animal toxicity data, clinical data,

Chemistry Manufacturing Control (CMC) data and other relevant information.

15. The applications for grant of permission to conduct clinical trials and permission to import or manufacture new drugs (here, COVID-19 vaccines) are evaluated by the CDSCO in consultation with Subject Expert Committee "**SEC**" consisting of domain experts, which comprises of medical experts from Microbiology, Pulmonology, Immunology, Paediatrics, Internal medicine etc.

16. It is submitted that, provisions of the Second Schedule to the Rules of 2019 which were exercised to examine grant / refusal of approval to Covid-19 vaccines is reproduced below. These provisions provide for relaxation, abbreviations, omission or deferment of data for a new drug.

> **"...**
>
> ***...(2) Special situations for a new drug where relaxation, abbreviations, omission or deferment of data may be considered***. –
>
> *(i) Depending on categories and nature of new drugs to be imported or manufactured for sale or clinical trial to be undertaken (viz. New Chemical Entity, biological products, similar biologics, approved new drug or new dosage form or new indication or new route of administration or new strength of already approved drugs, etc.,) requirements of chemical and pharmaceutical information, animal*

pharmacology and toxicology data, clinical data may differ. The requirements may also differ depending on the specific phase of clinical trial proposed to be conducted as well as clinical parameters related to the specific study drug.

(ii) For drugs intended to be used in life threatening or serious disease conditions or rare diseases and for drugs intended to be used in the diseases of special relevance to Indian scenario or unmet medical need in India, disaster or special defence use e.g. haemostatic and quick wound healing, enhancing oxygen carrying capacity, radiation safety, drugs for combating chemical, nuclear, biological infliction etc., following mechanism may be followed to expedite the development of new drug and approval process.

(A) Accelerated Approval Process: *Accelerated approval process may be allowed to a new drug for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of alternative treatments, provided that there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment.*

(a) In such case, the approval of the new drug may be based on data generated in clinical trial where surrogate endpoint shall be considered rather than using standard outcome measures such as survival or disease progression, which are reasonably likely to predict clinical benefit, or a clinical endpoint. These should be measurable earlier than irreversible morbidity or mortality (IMM) and reasonably likely to predict clinical benefit.

(b) After granting accelerated approval for such drug, the post marketing trials shall be required to validate the anticipated clinical benefit.

(c) Accelerated approval may also be granted to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease of special relevance to the country, and addresses unmet medical needs. This provision is intended to facilitate and expedite review of drugs so that an approved product can reach the therapeutic armamentarium expeditiously.

(d) If the remarkable efficacy is observed with a defined dose in the Phase II clinical trial of investigational new drug for the unmet medical needs of serious and life threatening diseases in the country, it may be considered for grant of marketing approval by the Central Licencing Authority based on Phase II clinical trial data. In such cases, additional post licensure studies may be required to be conducted after approval to generate the data on larger population to further verify and describe the clinical benefits, as per the protocol approved by the Central Licencing Authority.

(e) The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development. Early in development, such potential should be sufficiently demonstrated based on nonclinical models, a mechanistic rationale and pharmacologic data. Later in development, prior to new drug approval such potential should be demonstrated through clinical data to address an unmet medical need.

Explanation. - For the purpose of this clause, an unmet medical need is a situation where treatment or diagnosis of disease or condition is not addressed adequately by

available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).”

17. Applying the aforesaid provisions of the Second Schedule, the CDSCO, in detailed consultation and deliberation with the SEC and after examining the efficacy etc. of the vaccine and its effects granted permission for restricted emergency use of COVAXIN and COVISHIELD vaccines of Bharat Biotech International Ltd. and Serum Institute of India Ltd. respectively under the Accelerated Approval Process.

I. DETAILS AND PROCEDURE FOR CONSIDERATION APPROVAL

18. The details which can be placed in public domain and the procedure followed for scientifically considering grant or refusal of the approval given to Bharat Biotech and Serum Institute respectively are given below:

A. DETAILS OF APPROVAL OF COVID-19 VACCINE [BRAND NAME: COVAXIN] OF BHARAT BIOTECH INTERNATIONAL LIMITED APPROVED FOR RESTRICTED USE IN EMERGENCY SITUATION.

(i) ***Name of Vaccine:*** Whole Virion Inactivated Corona Virus Vaccine

(ii) ***Qualitative and Quantitative Composition:*** Each single human dose (0.5 mL) contains: Whole Virion Inactivated Corona Virus Antigen 6 micrograms produced using a Vero cell-based platform that propagates the virus, expressing the viral spike (S) protein of SARS-CoV-2.

(iii) ***Route of Administration:*** Intra Muscular (IM)

(iv) ***Indications:*** For active immunization to prevent COVID-19 caused by SARS-CoV-2 virusin individuals 18 years of age and older. The use of this vaccine should be in accordance with the official recommendation. This vaccine is permitted for restricted use in emergency situation in Clinical Trial mode, as per provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs & Cosmetics Act, 1940.

(v) ***Dose:*** Two doses on Day 0 and Day 28.

(vi) ***Process followed:***

a. In light of the urgent need emerging due to the COVID 19 pandemic in the country and to have earlier availability of vaccine, the CDSCO in detailed consultation and deliberations with SEC granted

permission to Bharat Biotech for conducting Phase I/II clinical trial of Whole Virion Inactivated Corona Virus Vaccine (COVAXIN) on 29.06.2020 & Phase III clinical trial on 23.10.2020.

b. The trials were registered on www.ctri.nic.in website as prescribed in the conditions for clinical trial permission.

A True copy of Clinical Trial Permissions and CTRI Registry is annexed herewith and marked as **ANNEXURE R/2** at pg. **177-189**.

c. Bharat Biotech then submitted interim safety and immunogenicity data of Phase I and II clinical trial carried out in the country along with safety data including Serious Adverse Events (SAE) data of the ongoing Phase III clinical trial in the country.

d. As per the interim report, in Phase I trial, 375 subjects of age ≥18 to ≤55 years were enrolled across the three groups and received three vaccine formulations, BBV152A (3µg with Algel-IMDG (Aluminium hydroxide gel- Imidazoquinolingall amide (IMDG); a TLR 7/8 agonist), BBV152B (6µg with Algel-IMDG), and BBV152C (6µg with Algel).

e. Among the 375 subjects who were administered the 1st dose, a total of 79 adverse events were recorded. Among the 368 subjects who were administered the 2nd dose, a total of 15 adverse events were recorded.

f. One serious adverse event was reported after the 1st dose which resulted in hospitalization due to Viral Pneumonitis.

g. Majority of the adverse events were either mild or moderate in severity. Pain at the injection site was the most commonly reported adverse event. These adverse effects were resolved without any sequelae and majority of adverse events, i.e. about 77.35% were resolved within 1 day.

h. The other commonly reported adverse events were headache, fever, pain at the injection site, followed by headache, fatigue, and fever.

i. The adverse events were seen in a total of 51 volunteers, which is about 13.6% of the volunteers.

j. For immunogenicity, both humoral and cell-mediated responses were observed. SARS-CoV-2 Antibody Responses (Anti S1, RBD, and N IgG) post 14 days after second dose along with IgG1/IgG4 ratio along

with spot-forming cells [SFCs], antigen-specific CD3+, CD4+, and CD8+Tcells (producing IFN-γ) were submitted by Bharat Biotech.

k. None of the participants had detectable neutralizing antibodies at baseline analyzed by MNT50.

l. The proportion of participants seroconverted post 2 weeks after 2nd dose were 87.9%, 91.9%, and 82.8% in the BBV152A, B, and C groups, respectively.

m. In Phase II trial, 380 subjects of age ≥12 to ≤65 years were enrolled among two groups and received two vaccine formulations, BBV152 A and BBV152B.

n. Among the 380 subjects, who were administered the 1st dose, a total of 51 adverse events were recorded, and after administering the 2nd dose, a total of 46 adverse events were recorded.

o. No serious adverse event was reported in Phase II study.

p. All the 97 adverse events were either mild or moderate in severity. Pain at the injection site was the most common reported adverse event. The other common adverse events reported were headache,

fever and rash. Most of the adverse effects being mild in nature were resolved without any sequelae and majority of adverse events about 86% resolved within 1 day. These 97 adverse events were reported in 65 volunteers, which is about 15.4% of the total volunteers.

q. Humoral responses measured by ELISA and Neutralization assays were also observed.

r. In Phase II clinical trial, SARS-CoV-2 Antibody Responses (Anti S1, RBD, and N IgG) post 14 days after second dose was evaluated. None of the participants had detectable neutralizing antibodies at baseline analyzed by MNT50. The proportion of seroconverted participants of Group 1 and Group 2, post 4 weeks of 2nd dose was 88.0% and 96.6% respectively.

s. The data was reviewed by CDSCO in consultation with SEC, comprising of eminent experts from Microbiology, Pulmonology, Immunology, Pediatrics, Internal medicine etc. in meetings dated 09.12.2020, 30.12.2020 and 02.01.2021. The SEC noted that the vaccine Inactivated Whole Virion and this Corona Virus Vaccine had the potential to target mutated corona virus strains.

t. The data generated till then demonstrated a strong immune response (both antibody as well as T cell) and in-vitro viral neutralization.

u. The ongoing clinical trial was a large trial on 25,800 Indian subjects in which already 22,500 subjects had been enrolled including subjects with co-morbid conditions as well those which had demonstrated safety till date.

v. Moreover, Bharat Biotech presented the safety and efficacy data from non-human primate challenge study also, where the vaccine was found to be safe and effective.

w. In view of above, after detailed deliberation, the SEC recommended for grant of permission for restricted use of Covaxin in emergency situation in public interest. As an abundant precaution, the vaccine was permitted in clinical trial mode, to ensure more options for vaccinations, especially in the context of an emerging threat of mutant strains.

x. Further, it was recommended that Bharat Biotech should continue the on-going Phase III clinical trial and submit data emerging from the trial as and when available.

y. Hence, after sufficient examination, CDSCO decided to accept the recommendations of the SEC and accordingly, permission was granted to Bharat Biotech to manufacture Whole Virion Inactivated Corona Virus Vaccine (COVAXIN) for restricted use in emergency situation in clinical trial mode with various conditions/restrictions on 03.01.2021.

It is respectfully submitted that all the above scientific steps of analysing scientific data were taken as per prescribed protocol and by bodies having domain expertise.

A True Copy of new drug permission is annexed herewith and marked as **ANNEXURE R/3** at pg. **190-191.**

z. In parallel, Bharat Biotech continued its Phase III clinical trial - a randomized, double-blind, phase 3 study, to evaluate the Efficacy, Safety and Immunogenicity of Whole-Virion Inactivated SARS-CoV-2 Vaccine in 25,800 Volunteers aged 18 years and above having approximate study duration of 12 months.

aa. The Phase 3 study followed randomized study participants for efficacy until virologically confirmed (RT-PCR positive) symptomatic COVID-19 participants which was eligible for the primary

efficacy analysis. After reaching the target number (n=130) of symptomatic COVID-19 cases, the study would continue to assess safety until the completion of the study duration.

bb. Bharat Biotech submitted the interim safety and efficacy data of phase III clinical trial of Whole Virion, Inactivated Corona Virus Vaccine (BBV152) to CDSCO which was reviewed in consultation with SEC (COVID-19) in meetings held on 08.03.2021 & 10.03.2021 respectively.

cc. The SEC noted that the firm had carried out interim analysis after 43 cases of symptomatic RT-PCR positive COVID-19 had been reported, out of which 36 were in the placebo arm and 7 in the vaccine arm.

dd. After detailed deliberation, the SEC recommended for omission of the condition of use of the Vaccine in clinical trial mode. However, it was recommended that the vaccine be continued to be used under restricted use in emergency situation condition.

ee. Further, the ongoing Phase III clinical trial should be continued as per the approved protocol and Bharat Biotech should update the prescribing information

and factsheet accordingly (under restricted use in emergency situation condition).

ff. All other conditions of the marketing authorization continued to remain the same.

gg. Accordingly, based on the recommendations of SEC, the condition "*This permission is for restricted use in emergency situation in public interest use in as an abundant precaution, in clinical trial mode*" as mentioned in the permission was amended to read as "*This permission is for restricted use in emergency situation in public interest*" by CDSCO letter dated 11.03.2021 with the condition to continue ongoing Phase III clinical trial as per approved clinical trial protocol.

hh. Subsequently, Bharat Biotech submitted updated interim safety & efficacy data of Phase III clinical trial of Whole Virion Inactivated SARS-CoV-2 Vaccine (BBV152) which was reviewed by CDSCO in consultation with SEC on 22.06.2021, wherein the SEC noted that the firm submitted safety & efficacy data till two months after the second dose along with final efficacy analysis after accrual of 130 cases of symptomatic RT-PCR positive COVID-19 as required to meet the primary endpoint.

ii. Out of 130 cases, 106 were reported in the placebo arm and 24 in the vaccine arm giving vaccine efficacy of 77.8%. The Committee also noted that currently Phase III clinical trials were ongoing.

jj. After detailed deliberation, the SEC recommended that the vaccine should be continued to be used under restricted use in emergency situation and the Phase III clinical trial should be continued as per the approved protocol. It was also recommended that the firm should update the prescribing information and factsheet accordingly and submit to CDSCO for approval.

kk. As per the information available, Phase I and Phase II clinical trial reports of Bharat Biotech are published in The Lancet Infectious Diseases Journal which is publicly available. M/s Bharat Biotech vide e-mail dated 06.07.2021 also informed that phase III trial publication titled '*Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a double-blind, randomised, controlled phase 3 trial*' was submitted to LANCET Journal on 02.07.2021.

A True copy of publications and manuscript of Phase III trial of Bharat Biotech is annexed herewith and marked **ANNEXURE R/4** at pg. **192-246.**

(vii) Further, the summary of clinical trials of Whole Virion Inactivated Corona Virus Vaccine (COVAXIN) is available in Summary of Product Characteristics (SmPC), Factsheet, prescribing Information submitted by Bharat Biotech at the time of grant of permission at www.cdsco.gov.in website.

A True copy of Factsheet and Summary of product Characteristics (SmPC) COVAXIN Vaccine is annexed herewith and marked as **ANNEXURE R/5 at** pg. **247-262.**

(viii) Further, while issuing the permission for restricted emergency use on 03.01.2021, Bharat Biotech was directed to upload updated Summary of Product Characteristics (SmPC), Factsheet, prescribing Information/ package insert on its website.

It is respectfully submitted that all the above scientific steps of analysing scientific data were taken as per prescribed protocol and by bodies having domain expertise.

B. DETAILS OF THE APPROVAL OF CHADOX1 NCOV-19 CORONA VIRUS VACCINE (RECOMBINANT) (COVISHIELD), MANUFACTURED BY SERUM INSTITUTEOF INDIA LTD. IN INDIA

FOR RESTRICTED USE IN EMERGENCY SITUATION ARE SUBMITTED AS BELOW:

(i) ***Name of Vaccine:*** ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)

(ii) ***Qualitative and Quantitative Composition:*** One dose (0.5 ml) contains: ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) 5×10^{10} viral particles (vp) Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells. This product contains genetically modified organisms (GMOs).

(iii) ***Route of Administration:*** Intra Muscular (IM)

(iv) ***Indications:*** For active immunization of individuals of ≥18 years old for the prevention of corona virus disease (COVID-19) when administered in two doses schedule. The second dose should be administered between 4 to 6 weeks after the first dose. However, there is data available for administration of the second dose up to 12 weeks after the first dose from the overseas studies.

(v) ***Process:***

a. Serum Institute developed ChAdOx1 nCOV-19 Corona Virus Vaccine (Recombinant) vaccine in collaboration with Oxford University & AstraZeneca under technology transfer. Being a technology transfer vaccine of Oxford/AstraZeneca, Serum Institute had conducted Phase II/III clinical trial in the country as the clinical development including Phase I trial was conducted in other countries.

b. In light of urgent need due to COVID-19 pandemic in the country and to have earlier availability of vaccine, CDSCO in consultation with SEC granted permission to Serum Institute to conduct Phase II/III clinical trial of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) on 02.08.2020.

A True copy of clinical trial permission and CTRI registry is annexed herewith and marked as **ANNEXURE R/6** at pg. **263-287.**

c. Serum Institute submitted the safety, immunogenicity & efficacy data of Phase II/III clinical trials of AstraZeneca vaccine carried out in UK, Brazil and South Africa along with the safety & immunogenicity data from the ongoing Phase II/III clinical trial in the country.

d. The SEC reviewed the proposal of restricted emergency use along with above details in its meetings dated 09.12.2020, 30.12.2020 and 01.01.2021 as well as continuously reviewed the data as and when received.

e. The Medicines and Healthcare Products Regulatory Authority (MHRA), United Kingdom's approval for AstraZeneca vaccine on 30.12.2020 along with its conditions/restrictions was also reviewed by the Committee.

f. Phase II/III clinical trial of Serum Institute was observer-blind, randomized, controlled study to determine the safety and immunogenicity of COVISHIELD as compared to Oxford vaccine & Placebo in 1600 healthy Indian adults with approximate follow up of 6 months.

g. In this trial, as on 14.12.2020 (cut-off date for marketing authorization permission by Serum Institute), all 1600 participants had received first dose and 1577 participants had received second dose. Overall, the incidence of solicited reactions (injection site reactions such as pain, tenderness, redness, warmth, itch, swelling and

induration; and systemic reactions include fever, chills, fatigue, malaise, headache, arthralgia and myalgia), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups. No causally related SAE was reported with the study vaccine.

h. At the time of approval, in its Phase II/III trial, Serum Institute evaluated SARS CoV-2 S-binding antibody response of COVISHIELD vaccine and data of 186 participants (140 subjects of COVISHIELD vaccine group and 46 subjects of Oxford/AZ-ChAdOx1 nCoV-19 vaccine group) post 28 days after second dose was submitted in the interim report wherein the Geometric Mean Titres (GMT) for Anti-S IgG antibodies were reported as 33331.6 in COVISHIELD vaccine and 33263.6 in Oxford/AZ-ChAdOx1 nCoV-19 vaccine group respectively with 100% seroconversion rates.

i. As per the efficacy and immunogenicity data from the overseas studies, COVID-19 Vaccine AstraZeneca efficacy against COVID-19 was reported to be 70.42% against COVID-19 cases and overall Geometric Mean Titers (GMT) of

SARS CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca, 28 days after second dose was reported to be 29034.74.

j. The SEC noted that the safety & immunogenicity data presented by the firm from the Indian study was comparable with that of the overseas clinical trial data.

k. Considering the seriousness of COVID-19 pandemic and the emergent situation, there was an urgent need of vaccine in the country. After detailed deliberation, SEC recommended for grant of permission for restricted emergency use of the vaccine subject to various regulatory provisions including with various conditions/restrictions.

l. After adequate examination, CDSCO decided to accept the recommendations of the SEC and accordingly, permission was granted to Serum Institute to manufacture ChAdOx1 nCOV-19 Corona Virus Vaccine (Recombinant) (COVISHIELD) for restricted use in emergency situation with various conditions/restrictions on 03.01.2021.

A True Copy of New Drug Permission is annexed herewith and marked as **ANNEXURE R/7** at pg. **288-289.**

It is respectfully submitted that all the above scientific steps of analysing scientific data were taken as per prescribed protocol and by bodies having domain expertise.

(vi) As per the information available, AstraZeneca has published the results of Safety and Efficacy data of overseas clinical trials of ChAdOx1 nCOV-19 Corona Virus Vaccine (Recombinant) in Lancet journal which is publicly available.

A True copy of publication of M/s AstraZeneca is annexed herewith and marked as **ANNEXURE R/8** at pg. **290-302.**

(vii) The summary of overseas and Phase II/III clinical trial of nCOV-19 Corona Virus Vaccine (Recombinant) conducted in the country is available in Summary of Product Characteristics (SmPC), Factsheet, prescribing Information submitted by Serum Institute, at the time of marketing authorization approval which are available on www.cdsco.gov.in website.

(viii) While issuing marketing authorization permission on 03.01.2021, Serum Institute was directed to upload updated Summary of Product Characteristics (SmPC), Factsheet, prescribing Information/ package insert on its website.

A True copy of Factsheet and Summary of product Characteristics (SmPC) COVISHIELD Vaccine is annexed herewith and marked as **ANNEXURE R/9** at pg. **303-322.**

It is respectfully submitted that all the above scientific steps of analysing scientific data were taken as per prescribed protocol and by bodies having domain expertise.

19. Therefore, it is submitted that approval to Covaxin and Covishield vaccines has been granted for restricted emergency use after following the procedure prescribed under Rules of 2019 and the Drugs and Cosmetics Act, 1940 and after detailed deliberations among eminent scientific experts, taking all precautions necessary, considering the Covid-19 pandemic. Therefore, all allegations and apprehensions raised by the Petitioner in its writ petition should be rejected based on the aforesaid submissions.

II. ***CLINICAL TRIALS & CLINICAL TRIAL DATA***

20. It is submitted that, Rule 25 of New Drugs and Clinical Trials Rules, 2019 provides various conditions of permission for conduct of clinical trial wherein, as per sub clause (v) clinical trial shall be registered with the Clinical Trial Registry of India maintained by the Indian Council of Medical Research before enrolling the first subject for the trial. As per subclause (vi) of Rule 25, clinical trial shall be conducted in accordance with the approved clinical trial protocol and other related documents and as per requirements of Good Clinical Practices (GCP) Guidelines and the provisions of Rules of 2019.

21. It is submitted that as provided by Rule 25(v), all clinical trials conducted in India are registered with the Clinical Trials Registry- India ("**CTRI**"), which is hosted at the ICMR's National Institute of Medical Statistics. This is a free and online public record system for registration of clinical trials being conducted in India and is readily accessible for public on its website www.ctri.nic.in. The Petitioner ought to have placed these facts on record.

22. Similarly, as provided under Rule 25(vi), the Expert Committee set up by CDSCO in consultation with clinical experts has formulated the Good Clinical Practices

Guidelines for generation of clinical data on drugs [hereinafter referred to as 'the Guidelines']

A True copy of the Good Clinical Practices for Clinical Research in India is annexed herewith and marked as **ANNEXURE R/10** at pg. **323-410.**

23. In the Guidelines, under subheading "2.4 Ethical & Safety Considerations", there is a specific subheading "2.4.1 Ethical Principles". The ethical principles identify the principles of privacy and confidentiality as an important principle for clinical trials and state:

> ***"d. Principles of privacy and confidentiality*** *whereby, the identity and records of the human subjects of the research or experiment are as far as possible kept confidential; and that no details about identity of said human subjects, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the human subject concerned, or someone authorized on their behalf; and after ensuring that the said human subject does not suffer from any form of hardship, discrimination or stigmatization as a consequence of having participated in the research or experiment."*

24. Further, the Guidelines in Para 2.4.4. prescribe "Essential Information on Confidentiality for Prospective Research Subjects Safeguarding Confidentiality", which is extracted below :

> ***"2.4.4. Essential Information on Confidentiality for Prospective Research Subjects***
> ***Safeguarding Confidentiality*** *- The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual subjects. Data of individual subjects can be disclosed only in a court of law under the orders of the presiding judge or in some cases may be required to communicate to drug registration authority or to health authority. Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed."*

25. In addition to the above, Chapter III of the Rules of 2019 refer to Ethics Committee for Clinical Trial, Bioavailability and Bioequivalence Study. Chapter III specifies the Requirements, Constitution, Registration, Validity, Renewal of registration, proceedings, maintenance of records, suspension and cancellation. The functions of the Ethics Committee are prescribed under Rule 11 and they include safeguarding the rights, safety and wellbeing of trial subjects in accordance with the rules. These Rules also empower the Ethics Committee to discontinue or suspend the clinical trial in case it concludes that the trial is likely to compromise the right, safety or wellbeing of the trial subject.

26. In addition, ICMR has published National Ethical Guidelines for Biomedical and Health Research involving human participants. These guidelines are applicable to all

biomedical, social and behavioral science research for health conducted in India involving human participants and is revised from time to time to incorporate new developments in the field of science and technology. The latest guideline has been revised and published in the year 2017.

27. As per the National Ethical Guidelines of ICMR, there are four basic ethical principles for conducting biomedical and health research – (i) respect for persons (autonomy), (ii) beneficence, (iii) non-malfeasance and (iv) justice. These four ethical principles been enunciated for protecting the dignity, rights, safety and well-being of research participants. These four basic principles have been expanded into 12 general principles which are to be applied to all biomedical, social and behavioral science research for health involving human participants. The principles are :-

(i) Principle of essentiality
(ii) Principle of voluntariness
(iii) Principle of non-exploitation
(iv) Principle of social responsibility
(v) Principle of ensuring privacy and confidentiality
(vi) Principle of risk minimization
(vii) Principle of professional competence
(viii) Principle of maximization of benefit
(ix) Principle of institutional arrangements
(x) Principle of transparency and accountability

(xi) Principle of totality of responsibility

(xii) Principle of environmental protection

28. Under Paragraph No. 1.1.5 of the National Ethical Guidelines of ICMR, "*Principle of ensuring privacy and confidentiality*" state :

> ***"1.1.5 Principle of ensuring privacy and confidentiality*** *whereby to maintain privacy of the potential participant, her/his identity and records are kept confidential and access is limited to only those authorized. However, under certain circumstances (suicidal ideation, homicidal tendency, HIV positive status, when required by court of law etc.) privacy of the information can be breached in consultation with the EC for valid scientific or legal reasons as the right to life of an individual supersedes the right to privacy of the research participant."*

29. Similarly, under Paragraph No. 2.3 of the National Ethical Guidelines of ICMR titled as "Privacy and Confidentiality", subheading no. 2.3.3 and 2.3.6 provide :

> *"2.3.3 Any publication arising out of research should uphold the privacy of the individuals by ensuring that photographs or other information that may reveal the individual's identity are not published. A specific re-consent would be required for publication, if this was not previously obtained.*
>
> *…*
>
> *2.3.6 Data of individual participants/community may be disclosed in certain circumstances with the*

permission of the EC such as specific orders of a court of law, threat to a person's or community's life, public health risk that would supersede personal rights to privacy, serious adverse events (SAEs) that are required to be communicated to an appropriate regulatory authority etc."

30. Further, the World Medical Association has developed the "Declaration of Helsinki" as statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. These include research on identifiable human material or identifiable data.

31. The latest statement adopted in 64th WMA General Assembly, Fortaleza, Brazil, October 2013 states, *inter alia* :

- *Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.*
- *In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.*
- *Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.*

32. Paragraph No. 24 "Privacy and Confidentiality" of the Declaration of Helsinki, 2013 states :

"24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information".

33. It is submitted that, Paragraph No. 35 and 36 "Research Registration and Publication and Dissemination of Results" of the Declaration of Helsinki, 2013 provides:

"35. every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication".

34. It is also submitted that Paragraph 1 (1.1) (vii) of Table 3 of Third Schedule of Rules of 2019 provide for "Informed Consent", wherein it has been provided that confidentiality of records identifying the subject would be maintained. Further, under Paragraph no. 2 (iii) of Table 3 of Third Schedule of the Rules of 2019 provide for "Informed

Consent" and this prescribes an informed consent form in which the Subject/Legally Acceptable Representative gives consent, that his / her identity will not be revealed in any information released to third parties or published. Under Paragraph 7 (xii) of Table 4 of Third Schedule of the Rules of 2019 - "Undertaking by the Investigator", the investigator undertakes to maintain confidentiality of the identification of all participating study patients and assure security and confidentiality of study data.

35. The aforesaid Guidelines, Principles and Rules have been referred to submit that clinical trial data which is in breach of the aforesaid cannot be made public. However, rest of clinical trial data that ought to be made public are already available in public domain, as is also evident from the submissions made in the present reply. Any submission of the Petitioner for disclosure of clinical trial data which would be in breach of the aforesaid rules and guidelines and which would expose any information on the participants of the clinical trial must be rejected.

III. EXPERT COMMITTEE MEETINGS

36. It is submitted that the recommendations of Subject Expert Committee (SEC) of all the meetings are uploaded on the website of CDSCO from time to time and no further disclosure as is being contended is required. A True copy of

recommendations of SEC for COVAXIN and COVISHIELD vaccines is annexed herewith and marked are as **ANNEXURE R/11** at pg. **411-421.**

37. It is further submitted that the detailed minutes of NTGAI meeting are already in public domain and can be downloaded through both ICMR &MoHFW website and no further disclosure is required. (https://main.mohfw.gov.in/Organisation/Departments-of-Health-and-Family-Welfare/immunization)

IV. VACCINATION AND ADVERSE EVENT FOLLOWING IMMUNISATION SURVEILLANCE SYSTEM IN INDIA

38. It is submitted that, the COVID 19 vaccination campaign was started in India on 16.01.2021. In the initial phase, the vaccines were offered to priority groups based on exposure and susceptibility to the COVID 19 disease. Therefore, it was initially provided to healthcare workers (16.01.2021) and frontline workers (01.02.2021), followed by the elderly (ages greater than 60 years of age) and people aged above 45 with co-morbidities from 01.03.2021 onwards. In the 3rd phase, from 01.04.2021, the population eligible to receive vaccines was expanded to include all people above 45 years of age. From 01.05.2021, all adults more than 18 years of age were eligible to receive vaccines. For lactating women, vaccination was allowed from 19.05.2021 and for pregnant women, from

02.07.2021. A True copy of the Revised Guidelines for Implementation of National Covid-19 Vaccination Program is annexed herewith and marked as **ANNEXURE R/12** at pg. **422-425.**

39. It is submitted that, the procedures and protocols for adverse event following immunization surveillance system in India are established under the National Adverse Event Following Immunisation Surveillance Guideline. The National Adverse Event Following Immunisation Surveillance Secretariat was established in the Immunization Technical Support Unit ("**ITSU**") in 2012. The National Adverse Event Following Immunisation Surveillance Secretariat had staff dedicated for managing Adverse Event Following Immunisation surveillance system. It was further strengthened by technical and subject experts from Lady Hardinge Medical College and Allied Hospitals in New Delhi which was nominated as the National Adverse Event Following Immunisation Surveillance Technical Collaborating Centre.

40. It is respectfully submitted that, under the existing National Adverse Event Following Immunisation Surveillance, there is a structure which consist of Adverse Event Following Immunisation ("**AEFI**") Committee at different levels like State and National Level, which provides guidance to the program and carries out documentation,

investigation and causality assessment besides training and orientation of health care workers and others involved in AEFI.

41. There is also an established protocol for reporting and causality assessment for any AEFI following vaccination with Universal Immunization Program (UIP) and Non-UIP vaccines.

42. The entire system of reporting AEFIs to State/ National level has been made paperless by enabling a web-based portal i.e. SAFEVAC (Surveillance and Action for Events Following Vaccination). This portal has allowed online reporting of all serious and severe adverse events following vaccinations at the district level.

43. The benefit of the web based portal is that case details are now entered, scanned copies of reports and records are uploaded and downloaded in SAFFEVAC. The portal also has facilities for generating dashboards and line-lists at different levels.

44. A similar feature for reporting of all AEFIs (including minor) by the vaccinator was made available in Co-WIN portal. At the district level, the DIOs were given the facility to report AEFI cases which have been shared with them from individuals who do not have access to Co-WIN.

Further investigations and sharing of hospital records, etc. can be done through Co-WIN by the DIO. A True copy of the Departmental Orders and Standard Operating Procedure is annexed herewith and marked as **ANNEXURE R/13** at pg. **426-427.**

45. It is humbly submitted that in order to ensure that the AEFI reporting mechanism is further strengthened, a strong convergence has been developed with the Pharmacovigilance Programme of India ("**PvPI**") under Indian Pharmacopoeia Commission ("**IPC**") for receipt of information regarding AEFI cases being reported from approximately 300 Adverse Drug Reaction Monitoring Centers in medical colleges and large hospitals throughout the country. Information from PvPI and Central Drug Control Standard Organisation (CDSCO) are collated and studied in case of any new, previously unknown events identified through AEFI surveillance.

46. The AEFI surveillance system of India successfully passed the assessment by global experts conducted by WHO in 2017 with highest possible maturity level ratings. See press release (Maximum Possible Marks to Indian NRA in WHO Assessment) dated 17 Feb 2017 under MOHFW at PIB press release archives: https://archive.pib.gov.in/archive2/erelease.aspx

A True copy of the Press Release dated 17.02.2017 is annexed herewith and marked as **ANNEXURE R/14** at pg. **428-429.**

47. It is humbly submitted that for Covid-19 vaccination, the same system of AEFI surveillance is being used. The surveillance system has been further strengthened for adult vaccination, especially for a novel vaccine which has been given only Emergency Use Authorization ("**EUA**").

48. Keeping in view the novel nature of the Covid 19 virus and adults as the target population, membership of National AEFI committee have been expanded to include Neurologists, Cardiologists, Respiratory Medicine Specialists and Medical Specialists. A True copy of the National AEFI Committee dated 08.12.2020 is annexed herewith and marked as **ANNEXURE R/15** at pg. **430-432.**

49. It is submitted that, the States/UTs have also been requested to expand the State/UT AEFI committee by including a Neurologist, Cardiologist, Respiratory Medicine Specialist, Medical Specialist and an Obstetrician-Gynecologist for strengthening AEFI surveillance for COVID 19 vaccinations. Once identified these specialists were trained on COVID-19 vaccination, AEFI surveillance and causality assessments on 08 and 09th Jan 2021.

A True copy of the Letter dated 04.01.2021 is annexed herewith and marked as **ANNEXURE R/16** at pg. **433-434.**

A True copy of the Letter dated 05.01.2021 is annexed herewith and marked as **ANNEXURE R/17** at pg. **435-436.**

50. It is submitted that, the causality assessment of AEFI cases is done at the State and National level by experts trained in causality assessment using the globally accepted causality assessment checklist, which is based on the definition and algorithm developed by WHO. Once approved by the experts of the National AEFI Committee, the results of causality assessment of AEFI cases are made available in the public domain (MOHFW website). These are shared with the States and districts for suitable action and also with the Central Drug Control Standard Organization under the Drug Controller General (India), for appropriate regulatory action.

51. In this regard, special groups have been constituted at the National level for focused causality assessments of serious and severe AEFI cases on a priority basis.

A True Copy of the Letter dated 11.02.2021 is annexed herewith and marked as **ANNEXURE R/18** at pg. **437-438.**

A True copy of the Letter dated 08.04.2021 is annexed herewith and marked as **ANNEXURE R/19** at pg. **439**.

52. The causality assessment of reported AEFI cases is a time-consuming process and hence a method of rapid review and assessment has been initiated at the National level to quickly review available information in each case and look for trends in reporting of specific events or unusual cases requiring further early investigation and assessment.

53. Besides the existing AEFI structure, a separate structure for Adverse Events of Special Interest ("**AESI**") was initiated to carry out active surveillance through sentinel sites.

V. CURRENT STATUS OF AEFI SURVEILLANCE FOR COVID 19 VACCINATION

54. It is submitted that, all cases of serious and severe AEFI [Adverse Event Following Immunisation], including reported death cases are subjected to scientific and technical review process. This process consists of rapid reviews, analysis and causality assessment done by a team of subject experts who have been trained for doing so. Only after the causality assessment has been done that the AEFI can be attributed to the vaccine. AEFI surveillance is a tool to identify and record all the possible adverse events following vaccination so that causality assessment can be done and adverse events actually caused by the vaccine

could be identified. Therefore, mere reporting of AEFI case should not be attributed to be caused by the vaccine unless proved by the causality assessment analysis.

55. It is submitted that these Adverse Event Following Immunisation is being monitored and reviewed. The percentage of such effect having serious / severe [including deaths] in case of both Covaxin and Covishield is less than 0.01%. This again is in the caveat that any such severe / serious effect including death cannot be attributed to vaccination. In all cases, it is respectfully submitted that the Central Government is conducting Rapid Review and Causality Assessment Of Serious And Severe AEFIS continuously.

VI. STATUS OF RAPID REVIEW AND CAUSALITY ASSESSMENT OF SERIOUS & SEVERE AEFIS

56. It is humbly submitted that 2116 serious and severe AEFI cases have been reported from 1,19,38,44,741 doses of COVID-19 vaccine administered till 24th Nov 2021. A report of rapid review and analysis completed for 495 (463 Covishield & 32 Covaxin) cases has been submitted. Another report of 1356 cases (1236 Covishield, 118 Covaxin & 2 Sputnik) serious and severe AEFI cases (including 495 cases already analysed) has been presented to NEGVAC. The rapid review and analysis of balance cases is underway and will be completed soon.

57. The links for information made available in public domain are mentioned below:

1- https://main.mohfw.gov.in/sites/default/files/Englishcovernote.pdf
2- https://main.mohfw.gov.in/sites/default/files/immunizationenglish30032021_0.pdf
3- https://main.mohfw.gov.in/sites/default/files/cassuliatyassesment11062021eng.pdf
4- https://main.mohfw.gov.in/sites/default/files/AEFI60casesreportenglish.pdf
5- https://main.mohfw.gov.in/sites/default/files/Englishnote.pdf
6- https://main.mohfw.gov.in/sites/default/files/aefienglish.pdf
7- https://main.mohfw.gov.in/sites/default/files/cassulityassesmentreportenglish.pdf
8- https://main.mohfw.gov.in/sites/default/files/english%20Covering.pdf
9- https://main.mohfw.gov.in/sites/default/files/englishimmunisationlist24112021.pdf

58. Some of the other relevant reports that are available in public domain are:-

Regarding report on bleeding and clotting events following COVID 19 vaccination in India with advisory:

https://www.pib.gov.in/PressReleseDetailm.aspx?PRID=1719293 – *'Bleeding and clotting events following COVID vaccination miniscule in India - National AEFI (Adverse Event Following Immunization) Committee submits report to the Union Health Ministry'* - Posted On: 17 MAY 2021 2:32PM by PIB Delhi

A True copy of the Press Release dated 17.05.2021 is annexed herewith and marked as **ANNEXURE R/20** at pg. **440-441.**

59. It is submitted that, clarification of reports of deaths following COVID 19 vaccination and process of causality assessment can be found at: https://pib.gov.in/PressReleasePage.aspx?PRID=1727196

COVID19 Vaccination: Myths Vs. Facts

60. It is submitted that, any death or hospitalization following vaccination cannot be automatically assumed to be due to vaccination; herein, causality assessments help to understand whether the "Adverse Event Following Immunization" was caused directly due to vaccine, and are conducted at State and national level for the investigated cases - Posted On: 15 JUN 2021 2:51PM by PIB Delhi.

Tweets by PIB regarding report on bleeding and clotting events following COVID 19 vaccination in India with advisory

61. It is submitted that the following tweets highlights bleedings and clotting events following the COVID-19 vaccination in India with advisory:

https://twitter.com/pib_india/status/1394582220367560704?lang=en

A True copy of the Press Release of PIB dated 15.06.2021 is annexed herewith and marked as **ANNEXURE R/21** at pg. **442-443.**

62. Therefore, it is submitted that there is continuous monitoring and examination of AEFI cases in India and any contrary submissions made by the writ petitioner in the writ petition are denied as incorrect and without adequate knowledge of all facts.

VII. ***MANDATING USE OF VACCINES***

63. The Central Government has formulated a detailed policy document providing broad vision of government regarding Covid-19 vaccination programme, under the title "Covid-19 Vaccine Operational Guidelines". This document

is on the website of the Central Government from the date it was made. This programme takes care of the pandemic situation as on the date of this Affidavit.
https://www.mohfw.gov.in/pdf/COVID19VaccineOG111Chapter16.pdf

64. In so far as the Petitioner's submissions regarding Covid 19 vaccine being mandatory, as per the Operational Guidelines document, COVID-19 vaccination is voluntary. However, it is emphasised and encouraged that all individuals take vaccination for public health and in his / her interest as well as public interest since in case of pandemic, an individual's ill health has a direct effect on the society. Covid-19 vaccination is also not linked to any benefits or services. Therefore, any submissions made by the Petitioner to the contrary, in so far as the Answering Respondents are concerned, is denied.

VIII. INDEMNIFICATION OF VACCINE MANUFACTURERS

65. No indemnity has been granted and the current legal regime under the New Drugs and Clinical Trials Rules, 2019 and Drugs and Cosmetics Act, 1940 does not contain any such provisions.

IX. PARLIAMENTARY STANDING COMMITTEE AND CDSCO:

66. In the report of the Hon'ble Parliamentary Standing Committee (PSC) during their review of functioning of CDSCO, the PSC examined the mandate and structure of CDSCO, qualification and powers of Drugs Controller General (India) [DCG(I)], role of the State Drug Regulatory Authority, capacity building of CDSCO and Central & State Drug Testing Laboratories, Infrastructure at Airport and Sea Port, New Drugs approval, Drugs withdrawn/discarded/banned abroad but available in the country, issue of granting licences by the States on Fixed Dose Combinations without approval of DCG (I), Drug Technical Advisory Board (DTAB), issues regarding similar brand names, Post marketing surveillance, Pharmacovigilance, updation on information of marketed drugs, spurious/sub-standard drugs, advertisement of prescription drugs in lay media and consumer information and clinical trial on new drugs.

67. The Ministry of Health and Family Welfare submitted its action taken reply on the above mentioned report on 28.12.2012.

68. In the reply, the Ministry submitted the details of various steps taken to strengthen Drug Regulatory System including the measures taken to streamline the process of

New Drug approval and recommendations of Dr. Katoch Committee of experts constituted by the Ministry to examine the validity of the scientific and statutory basis adopted for the approval of New Drug without Clinical Trial pointed-out in the 59th report, etc.

69. The Hon'ble Parliamentary Standing Committee then considered the action taken replies and made various recommendations for implementation in its 66th report. Since then the matter relating to drug regulatory structures being made more efficient has been examined by a number of Committees. Necessary follow up action has been taken on the findings and recommendations of those Committees. The recommendations made by Dr. Katoch Committee were further gone into by Prof. Ranjit Roy Chaudhory Committee and various recommendations have been implemented.

70. CDSCO has since been strengthened and a number of measures have been taken to address issues, including online submission and processing of various applications under SUGAM portal, notification of Medical Devices Rules, 2017 and New Drugs and Clinical Trials Rules, 2019, guidelines for biosimilars, evaluation of applications of clinical trials, new drugs and Investigational New Drug (IND) including r-DNA derived products and vaccines, new medical devices in consultation with Subject Experts Committees, various amendments in Drugs and Cosmetics

Rules including amendment for prohibition of advertisement of Schedule H, H1 & X drugs, provisions to address issues related to similar brands, action addressing issues on FDCs, measures to ensure quality of drugs, etc. as well as strengthening of infrastructure and manpower of CDSCO.

71. Based on the aforesaid reply, it is submitted that Covaxin & Covishield vaccines clinical trials were registered at www.ctri.nic.in. Clinical Trials Registry- India (CTRI), hosted at the ICMR's National Institute of Medical Statistics, which is a free and online public record system for registration of clinical trials being conducted in India, which is readily accessible for public.

72. Procedure prescribed under the Drugs and Cosmetics Act, 1940 and Rules of 2019 were strictly followed while granting permission to Covaxin and Covishield vaccines.

73. The ICMR guidelines and Declaration of Helsinki clearly mention to maintain privacy of the potential participant; her/his identity and records are kept confidential subject to certain exceptions as stated therein.

74. Neither the Rules of 2019, nor the GCP guidelines, ICMR guidelines, Declaration of Helsinki prescribe that the publication of the clinical trial study reports of each

participating clinical trial sites is mandatory before approval of any new drugs including vaccine.

75. The Summary of Product Characteristics (SmPC), Factsheet, prescribing Information submitted by firm at the time of marketing authorization approval are available on the website of CDSCO at the URL, www.cdsco.gov.in which contains summary details of clinical trial data and results, moreover, these trials are also registered on Clinical Trial Registry of India, maintained by ICMR which contains the trial details and data in public domain.

76. The clinical data generated in a clinical trial resides with the sponsor of the clinical trial and the data is submitted to the regulatory authorities for obtaining various permissions/licenses etc. The regulatory authority may verify the veracity of the data submitted. However, there is no regulatory provisions under which the regulatory authorities can direct the sponsor to place the full clinical trial data in public domain.

77. To summarize, it is humbly submitted that all data relating to clinical trial, approval by DCGI and vaccination data that is required to be and can be released as per law is already available in the public domain. The minutes of meetings and committee deliberations to the extent permissible are already in the public domain. Decision

regarding approval of Covid 19 vaccines have been taken by expert committees consisting of domain experts based on and after verifying data / information supplied by the manufacturers and after considering its efficacy and safety. Post vaccination adverse data is already in the public domain and the concerned authorities are continuously monitoring and examining this data. The Central Government has not mandated for Covid 19 vaccines to be administered mandatorily at this stage.

78. In light of the aforesaid submissions, it is submitted that the writ petition filed by the Petitioner deserves to be dismissed.

79. The Answering Respondents reserve their right to file detailed para wise reply at an appropriate stage of the proceedings.

80. The Answering Respondents submit accordingly.

Dr. P. B. N. PRASAD
Joint Drugs
DEPONENT
Central Drugs Standard Control Organisation
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O., New Delhi-110002

VERIFICATION:

I, the Deponent above-named, do hereby verify the contents of the above-mentioned Affidavit as being correct to the best of my knowledge and information and state that nothing material has been kept concealed therefrom.

Verified at New Delhi on the 28th day of November, 2021.

Dr. P. B. N. PRASAD
Joint Drugs
DEPONENT
Central Drugs Standard Control Organisation
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O., New Delhi-110002

MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health and Family Welfare)

NOTIFICATION

New Delhi, the 19th March, 2019

G.S.R.227(E) .— WHEREAS the draft of the New Drugs and Clinical Trials Rules, 2018 was published, in exercise of the powers conferred by sub-section (1) of section 12 and sub-section (1) of section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), in the Gazette of India, Extraordinary, Part II, section 3, sub-section (i) *vide* notification number G.S.R. 104(E), dated the 1st February, 2018, by the Central Government, after consultation with the Drugs Technical Advisory Board, inviting objections and suggestions from all persons likely to be affected thereby, before the expiry of a period of forty-five days from the date on which copies of the Official Gazette containing the said notification were made available to the public;

AND WHEREAS, copies of the Official Gazette containing the said notification were made available to the public on the 7th February, 2018;

AND WHEREAS, all objections and suggestions received in response to the said draft notification have been duly considered by the Central Government;

AND WHEREAS, the Hon'ble Supreme Court of India in Writ Petition(s) (Civil) No (s). 33/2012 Swathaya Adhikar Manch, Indore and another Versus Union of India and others with W.P.(C) No. 79/2012 (PIL-W), *inter alia,* observed that new clinical trial rules shall be finalised urgently;

NOW, THEREFORE, in exercise of the powers conferred by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules, namely:—

CHAPTER I

PRELIMINARY

1. Short title, commencement and applicability.— (1) These rules may be called the New Drugs and Clinical Trials Rules, 2019.

(2) They shall come in to force from the date of their publication in the Official Gazette, except Chapter IV which shall come in to force after one hundred and eighty days.

(3) They shall apply to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study and Ethics Committee.

2. Definitions.— (1) In these rules, unless the context otherwise requires,—

(a) "academic clinical trial" means a clinical trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the Central Licencing Authority or regulatory authority of any country for marketing or commercial purpose;

(b) "Act" means the Drugs and Cosmetics Act, 1940 (23 of 1940);

(c) "active pharmaceutical ingredient" means any substance which can be used in a pharmaceutical formulation with the intention to provide pharmacological activity; or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease; or to have direct effect in restoring, correcting or modifying physiological functions in human beings or animals;

(d) "adverse event" means any untoward medical occurrence (including a symptom or disease or an abnormal laboratory finding) during treatment with an investigational drug or a pharmaceutical product in a patient or a trial subject that does not necessarily have a relationship with the treatment being given;

(e) "bioavailability study" means a study to assess the rate and extent to which the drug is absorbed from a pharmaceutical formulation and becomes available in the systemic circulation or availability of the drug at the site of action;

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(f) "bioequivalence study" means a study to establish the absence of a statistically significant difference in the rate and extent of absorption of an active ingredient from a pharmaceutical formulation in comparison to the reference formulation having the same active ingredient when administered in the same molar dose under similar conditions;

(g) "bioavailability and bioequivalence study centre" means a centre created or established to undertake bioavailability study or bioequivalence study of a drug for either clinical part or for both clinical and analytical part of such study;

(h) "biomedical and health research" means research including studies on basic, applied and operational research or clinical research, designed primarily to increase scientific knowledge about diseases and conditions (physical or socio-behavioral); their detection and cause; and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation but does not include clinical trial as defined in clause (j);

(i) "Central Licencing Authority" means the Drugs Controller, India as referred to in rule 3;

(j) "clinical trial" in relation to a new drug or investigational new drug means any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its,-

(i) clinical or;

(ii) pharmacological including pharmacodynamics, pharmacokinetics or;

(iii) adverse effects,

with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug;

(k) "clinical trial protocol" means a document containing the background, objective, rationale, design, methodology including matters concerning performance, management, conduct, analysis, adverse event, withdrawal, statistical consideration and record keeping pertaining to clinical trial;

(l) "clinical trial site" means any hospital or institute or any other clinical establishment having the required facilities to conduct a clinical trial;

(m) "efficacy" in relation to a drug means its ability to achieve the desired effect in a controlled clinical setting;

(n) "effectiveness" in relation to a drug means its ability to achieve the desired effect in a real world clinical situation after approval of the drug;

(o) "Ethics Committee" means, for the purpose of, -

(i) clinical trial, Ethics Committee, constituted under rule 7 and registered under rule 8;

(ii) biomedical and health research, Ethics Committee, constituted under rule 16 and registered under rule 17;

(p) "Good Clinical Practices Guidelines" means the Good Clinical Practices Guidelines for conduct of clinical studies in India, formulated by the Central Drugs Standard Control Organisation and adopted by the Drugs Technical Advisory Board;

(q) "global clinical trial" means any clinical trial which is conducted as part of a clinical development of a drug in more than one country;

(r) "investigational new drug" means a new chemical or biological entity or substance that has not been approved for marketing as a drug in any country;

(s) "investigational product" means the pharmaceutical formulation of an active ingredient or placebo being tested or used in a clinical trial;

(t) "investigator" means a person who is responsible for conducting clinical trial at the clinical trial site;

(u) "medical management" means treatment and other necessary activities for providing the medical care to complement the treatment;

(v) "new chemical entity" means any substance that has not been approved for marketing as a drug by a drug regulatory authority of any country including the authorities specified under these rules and is proposed to be developed as a new drug for the first time by establishing its safety and efficacy;

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(w) "new drug" means,—

(i) a drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made thereunder, as per conditions specified in the labelling thereof and has not been approved as safe and efficacious by the Central Licencing Authority with respect to its claims; or

(ii) a drug approved by the Central Licencing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or

(iii) a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or

(iv) a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or

(v) a vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;

Explanation.— The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs for a period of four years from the date of their permission granted by the Central Licencing Authority and the drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs;

(x) "orphan drug" means a drug intended to treat a condition which affects not more than five lakh persons in India;

(y) "pharmaceutical formulation" means any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives, that is formulated to produce a specific physical form, such as, tablet, capsule or solution, suitable for administration to human or animals;

(z) "pharmacovigilance" means the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug- related problem;

(aa) "phytopharmaceutical drug" means a drug of purified and standardised fraction, assessed qualitatively and quantitatively with defined minimum four bio- active or phytochemical compounds of an extract of a medicinal plant or its part, for internal or external use on human beings or animals, for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include drug administered through parenteral route;

(bb) "placebo" means an inactive substance visually identical in appearance to a drug being tested in a clinical trial;

(cc) "post-trial access" means making a new drug or investigational new drug available to a trial subject after completion of clinical trial through which the said drug has been found beneficial to a trial subject during clinical trial, for such period as considered necessary by the investigator and the Ethics Committee;

(dd) "registered pharmacist" shall have the meaning as assigned to it in clause(i) of section 2 of the Pharmacy Act, 1948 (8 of 1948);

(ee) "Schedule" means the Schedule annexed to these rules;

(ff) "serious adverse event" means an untoward medical occurrence during clinical trial resulting in death or permanent disability, or hospitalisation of the trial subject where the trial subject is an outdoor patient or a healthy person, prolongation of hospitalisation where the trial subject is an indoor-patient, persistent or significant disability or incapacity, congenital anomaly, birth defect or life threatening event;

(gg) "similar biologic" means a biological product which is similar in terms of quality, safety and efficacy to reference biological product licenced or approved in India, or any innovator product approved in International Council of Harmonisation (ICH)member countries;

(hh) "sponsor" includes a person, a company or an institution or an organisation responsible for initiation and management of a clinical trial;

(ii) "State Licencing Authority" means Licencing Authority appointed by a State Government having qualifications specified in rule 49A of the Drugs and Cosmetics Rules, 1945;

(jj) "trial subject" means a person who is either a patient or a healthy person to whom investigational product is administered for the purposes of a clinical trial.

(2) Words and expressions used in these rules but not defined herein but defined in the Drugs and Cosmetics Act, 1940 (23 of 1940) shall have the meaning assigned to them in the Act.

CHAPTER II

AUTHORITIES AND OFFICERS

3. Central Licencing Authority.— The Drugs Controller, India appointed by the Central Government in the Ministry of Health and Family Welfare shall be the Central Licencing Authority for the purposes of these rules.

4. Delegation of powers of Central Licencing Authority.— (1) The Drugs Controller, India, with the prior approval of the Central Government, may, by an order in writing, delegate all or any of powers of the Central Licencing Authority to any other officer of the Central Drugs Standard Control Organisation not below the rank of Assistant Drugs Controller (India).

(2) The officer to whom the powers have been delegated under sub-rule (1) shall exercise all or any of the powers of the Central Licencing Authority under its name and seal.

5. Controlling Officer.— (1) The Drugs Controller, India may designate any officer not below the rank of Assistant Drugs Controller (India) as Controlling Officer.

(2) The Drugs Controller, India shall, by order, specify the areas and powers of the Controlling Officer.

(3) The Controlling Officer, designated under sub-rule (1) shall supervise the work of subordinate officers and shall exercise powers and perform functions which may be assigned to that Officer.

CHAPTER III

ETHICS COMMITTEE FOR CLINICAL TRIAL, BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

6. Requirement of the Ethics Committee.— (1) Whoever intends to conduct clinical trial or bioavailability study or bioequivalence study shall be required to have approval of an Ethics Committee for clinical trial registered under rule 8.

(2) The Ethics Committee shall apply for registration with the Central Licencing Authority under rule 8.

7. Constitution of Ethics Committee for clinical trial.— (1) The Ethics Committee shall have a minimum of seven members from medical, non-medical, scientific and non-scientific areas with at least**,—**

(i) one lay person;

(ii) one woman member;

(iii) one legal expert;

(iv) one independent member from any other related field such as social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian.

(2) The Ethics Committee referred to in sub-rule(1) shall consist of at least fifty percent of its members who are not affiliated with the institute or organization in which such committee is constituted.

(3) One member of the Ethics Committee who is not affiliated with the institute or organization shall be the Chairperson, and shall be appointed by such institute or organisation.

(4) One member who is affiliated with the institute or organization shall be appointed as Member Secretary of the Ethics Committee by such Institute or organization.

(5) The committee shall include at least one member whose primary area of interest or specialisation is non-scientific and at least one member who is independent of the institution.

(6) The members of the Ethics Committee shall follow the provisions of these rules, Good Clinical Practices Guidelines and other regulatory requirements to safeguard the rights, safety and well-being of trial subjects.

(7) Every member of the Ethics Committee shall be required to undergo such training and development programmes as may be specified by the Central Licencing Authority from time to time:

Provided that any member, who has not successfully completed such training and developmental programmes, shall be disqualified to hold the post of member of the Ethics Committee and shall cease to be a member of such committee.

(8) The members representing medical scientists and clinicians shall possess at least post graduate qualification in their respective area of specialisation, adequate experience in the respective fields and requisite knowledge and clarity about their role and responsibility as committee members.

(9) As far as possible, based on the requirement of research area such as Human Immunodeficiency Virus (HIV) or genetic disorder, specific patient group may also be represented in the Ethics Committee.

(10) No member of an Ethics Committee, having a conflict of interest, shall be involved in the oversight of the clinical trial or bioavailability or bioequivalence study protocol being reviewed by it and all members shall sign a declaration to the effect that there is no conflict of interest.

(11) While considering an application which involves a conflict of interest of any member of the Ethics Committee, such member may voluntarily withdraw from the Ethics Committee review meeting, by expressing the same in writing, to the Chairperson.

(12) The details in respect of the conflict of interest of the member shall be duly recorded in the minutes of the meetings of the Ethics Committee.

8. Registration of Ethics Committee relating to clinical trial, bioavailability and bioequivalence study.— (1) Every Ethics Committee, constituted under rule 7, shall make an application for grant of registration to the Central Licencing Authority in Form CT-01.

(2) The Ethics Committee shall furnish such information and documents as specified in Table 1 of the Third Schedule along with the application made in Form CT-01.

(3) The Central Licencing Authority,—

(i) shall scrutinise the information and documents furnished with the application under sub-rule (2); and

(ii) make such further enquiry, if any, considered necessary and after being satisfied, that the requirements of these rules have been complied with, may grant registration to Ethics Committee in Form CT-02; and if the Central Licencing Authority is not satisfied with the compliance of these rules by the applicant Ethics Committee, it may, reject the application, for reasons to be recorded in writing, within a period of forty-five working days, from the date of the receipt of the application made under sub-rule (1).

(4) An applicant Ethics Committee aggrieved by the decision of rejection of the application by the Central Licencing Authority under clause (ii) of sub-rule (3), may file an appeal before the Central Government in the Ministry of Health and Family Welfare within sixty working days from the date of the receipt of order of such rejection.

(5) The Central Government may, after such enquiry, as considered necessary, and after giving an opportunity of being heard to the appellant referred to in sub-rule (4), shall dispose of the appeal filed under that sub-rule within a period of sixty working days from the date on which the appeal has been filed.

9. Validity period of registration of Ethics Committee for clinical trial.— The registration granted in Form CT-02 shall remain valid for a period of five years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

10. Renewal of registration of Ethics Committee for clinical trial.— (1) On expiry of the validity period of registration granted under rule 9, an Ethics Committee may make an application for renewal of registration in Form CT-01 along with documents as specified in Table 1 of the Third Schedule ninety days prior to the date of the expiry of the registration:

Provided that if the application for renewal of registration is received by the Central Licencing Authority ninety days prior to the date of expiry, the registration shall continue to be in force until an order is passed by the said authority on such application:

Provided also that fresh set of documents shall not be required to be furnished, if there are no changes in such documents furnished at the time of grant of registration, and the applicant renders a certificate to that effect indicating that there is no change.

(2) The Central Licencing Authority shall, after scrutiny of information furnished with the application and after taking into account the inspection report, if any, and after such further enquiry, as considered necessary, and on being satisfied that the requirements of these rules have—

(i) been complied with, renew the registration of Ethics Committee in Form CT-02;

(ii) not been complied with, reject the application, for reasons to be recorded in writing, within a period of forty-five working days from the date of renewal application made under sub-rule (1).

11. Functions of Ethics Committee.— The Ethics Committee for clinical trial shall perform the following functions for a person, institution or organization; namely:—

(i) review and accord approval to a clinical trial, bioavailability or bioequivalence study protocol and other related documents, as the case may be, in the format specified in clause (B) of Table 1 of the Third Schedule and oversee the conduct of clinical trial to safeguard the rights, safety and wellbeing of trial subjects in accordance with these rules, Good Clinical Practices Guidelines and other applicable regulations;

(ii) make at appropriate intervals, an ongoing review of the clinical trials for which it has accorded approval and such review may be based on periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or by visiting the study sites;

(iii) indicate the reasons that weighed with it while rejecting or asking for a change or notification in the protocol in writing and a copy of such reasons shall also be made available to the Central Licencing Authority;

(iv) where any serious adverse event occurs to a trial subject or to study subject during clinical trial or bioavailability or bioequivalence study, the Ethics Committee shall analyse the relevant documents pertaining to such event and forward its report to the Central Licencing Authority and comply with the provisions of Chapter VI;

(v) where at any stage of a clinical trial, it comes to a conclusion that the trial is likely to compromise the right, safety or wellbeing of the trial subject, the committee may order discontinuation or suspension of the clinical trial and the same shall be intimated to the head of the institution conducting clinical trial and the Central Licencing Authority;

(vi) allow any officer authorised by the Central Licencing Authority to enter, with or without prior notice, to inspect the premises, any record, or any documents related to clinical trial, furnish information to any query raised by such authorised person, in relation to the conduct of clinical trial and to verify compliance with the requirements of these rules, Good Clinical Practices Guidelines and other applicable regulations for safeguarding the rights, safety and well-being of trial subjects;

(vii) comply with the requirements or conditions in addition to the requirements specified under the Act and these rules as may be specified by the Central Licencing Authority with the approval of the Central Government, to safeguard the rights of clinical trial subject or bioavailability or bioequivalence study subject.

12. Proceedings of Ethics Committee for clinical trial.— (1) No clinical trial or bioavailability or bioequivalence protocol and related documents shall be reviewed by an Ethics Committee unless at least five of its members as detailed below are present, namely:—

(i) medical scientist (preferably a pharmacologist);

(ii) clinician;

(iii) legal expert;

(iv) social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person;

(v) lay person.

(2) The Ethics Committee may constitute one or more sub-committees of its members to assist in the functions assigned to it.

(3) The Ethics Committee may associate such experts who are not its members, in its deliberations but such experts shall not have voting rights, if any.

(4) Any change in the membership or the constitution of the registered Ethics Committee shall be intimated in writing to the Central Licencing Authority within thirty working days.

13. Maintenance of records by Ethics Committee for clinical trial.— (1) The Ethics Committee shall maintain data, record, registers and other documents related to the functioning and review of clinical trial or bioavailability study or bioequivalence study, as the case may be, for a period of five years after completion of such clinical trial.

(2) In particular and without prejudice to the generality of the sub-rule (1), the Ethics Committee shall maintain the following records for a period of five years after completion of every clinical trial or bioavailability study or bioequivalence study, namely:-

(i) the constitution and composition of the Ethics Committee;

(ii) the curriculum vitae of all members of the Ethics Committee;

(iii) standard operating procedures followed by the Ethics Committee;

(iv) national and international guidelines followed by the Ethics Committee;

(v) copies of the protocol, data collection formats, case report forms, investigators brochures, etc., submitted for review;

(vi) all correspondence with committee members and investigators regarding application, decision and follow up;

(vii) agenda of all Ethics Committee meetings and minutes of all Ethics Committee meetings with signature of the Chairperson;

(viii) copies of decisions communicated to applicants;

(ix) records relating to any order issued for premature termination of study with a summary of the reasons thereof;

(x) final report of the study including microfilms, compact disks or video recordings;

(xi) recommendation given by Ethics Committee for determination of compensation;

(xii) records relating to the serious adverse event, medical management of trial subjects and compensation paid.

(3) The Ethics Committee shall furnish the information maintained under sub-rule (1) and sub-rule (2), as and when required by the Central Licencing Authority or any other officer authorised on its behalf.

14. Suspension or cancellation of registration of Ethics Committee for clinical trial.— (1) Where Central Licencing Authority is of the opinion that any Ethics Committee fails to comply with any provision of the Act or these rules, it may issue show cause notice to such Ethics Committee specifying therein such non-compliances and the period within which reply shall be furnished by such Ethics Committee.

(2) On receipt of reply for the show cause notice within a period specified in the show cause notice, the Central Licencing Authority may give an opportunity of being heard, in person to such Ethics Committee.

(3) After consideration of the facts and reply given by the Ethics Committee under sub-rule (2), the Central Licencing Authority, may take one or more of the following actions, namely:-

(i) withdraw show cause notice issued under sub-rule(1);

(ii) issue warning to the Ethics Committee describing the deficiency or defect observed during inspection or otherwise, which may adversely affect the rights or well-being of the trial subject or the validity of clinical trial or bioavailability or bioequivalence study being conducted;

(iii) reject the results of clinical trial or bioavailability and bioequivalence study;

(iv) suspend for such period as considered appropriate or cancel the registration issued under rule 8;

(v) debar its members to oversee any clinical trial in future for such period as may be considered appropriate by the Central Licencing Authority.

(4) Where the Ethics Committee or any member of the Ethics Committee is aggrieved by an order of the Central Licencing Authority under sub-rule (3), such aggrieved Ethics Committee or member, may, within a period of sixty working days of the receipt of the order, file an appeal to the Central Government.

(5) Where an appeal has been filed under sub-rule (4), the Central Government may, after such enquiry, as it thinks necessary, and after giving an opportunity of being heard, pass such order in relation thereto as it thinks appropriate in the facts and circumstances of the case within a period of sixty working days from the date of filing of the appeal.

CHAPTER IV

ETHICS COMMITTEE FOR

BIOMEDICAL AND HEALTH RESEARCH

15. Ethics Committee for biomedical and health research.— Any institution or organisation which intends to conduct biomedical and health research shall be required to have an Ethics Committee to review and oversee the conduct of such research as detailed in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

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16. Constitution of Ethics Committee for biomedical and health research.— (1) The Ethics Committee referred to in rule 15, relating to biomedical and health research shall be constituted in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants as may be specified by the Indian Council of Medical Research from time to time and shall function in accordance with said guidelines.

(2) The Ethics Committee referred to in sub-rule (1), shall review the work of the biomedical and health research centre before initiation and oversee throughout the duration of the biomedical and health research as per National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

(3) An institution or organisation or any person shall conduct any biomedical and health research with the approval of the Ethics Committee for biomedical and health research registered under rule 17.

(4) Any biomedical and health research shall be conducted in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants as may be specified by the Indian Council of Medical Research from time to time.

(5) Institutions desirous of conducting biomedical and health research as well as clinical trials or bioavailability or bioequivalence study shall require obtaining registration from specified authorities as provided in rule 8 and rule 17.

17. Registration of Ethics Committee related to biomedical and health research.—

(1) An Ethics Committee constituted under rule 16, shall be required to register with the authority designated by the Central Government in the Ministry of Health and Family Welfare, Department of Health Research under these rules for which an application shall be made in Form CT-01 to the said authority.

(2) The application referred to in sub-rule (1) shall be accompanied with the information and documents as specified in Table 1 of the Third Schedule.

(3) On receipt of application in Form CT-01 under sub-rule (1), the authority designated under sub-rule (1) shall grant provisional registration which shall remain valid for a period of two years.

(4) After the grant of provisional registration under sub-rule (3), the authority designated under sub-rule (1) shall scrutinise the documents and information furnished with the application, and if satisfied that the requirements of these rules have been complied with, grant final registration to Ethics Committee in Form CT-03; or if not satisfied, reject the application, for reasons to be recorded in writing and the final registration in Form CT-03 shall supersede the provisional registration granted under sub-rule (3).

(5) An applicant who is aggrieved by the decision of the authority designated under sub-rule (1), may file an appeal within sixty working days from the date of receipt of such rejection before the Central Government in the Ministry of Health and Family Welfare, and the Central Government, may, after such enquiry as is considered necessary in the facts and circumstances of the case, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

(6) The Ethics Committee shall make an application for renewal of registration in Form CT-01 along with documents as specified in sub-rule (2) at least ninety days prior to the date of the expiry of its final registration:

Provided that if the application for renewal of registration is received by the authority designated under sub-rule (1), ninety days prior to the date of expiry, the registration shall continue to be in force until an order is passed by the said authority on the application:

Provided further that fresh set of documents shall not be required to be furnished, if there are no changes in such documents furnished at the time of grant of final registration, and if the applicant renders a certificate to that effect indicating that there is no change.

(7) The authority designated under sub-rule (1) shall after scrutiny of information furnished with the application and after such further enquiry, as considered necessary and on being satisfied that the requirements of these rules have been complied with, renew the registration of Ethics Committee in Form CT-03, or if not reject the application, for reasons to be recorded in writing.

(8) The authority shall take a decision under sub-rule (7) within a period of forty-five working days, from the date of application made under sub-rule(1).

(9) The registration granted in Form CT-03 shall remain valid for a period of five years from the date of its issue, unless suspended or cancelled by the authority designated under sub-rule (1).

(10) The function, proceedings of ethics committee and maintenance of records shall be as per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

(11) In case there is a change in composition of registered Ethics Committee in an institution it shall be reported to the authority designated under sub-rule (1).

18. Suspension or cancellation of registration of Ethics Committee for biomedical and health research.— (1) Subject to provisions of rule 17, where the Ethics Committee fails to comply with any provision of these rules, the authority designated under sub-rule (1), may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) issue warning to the Ethics Committee describing the deficiency or defect observed, which may adversely affect the rights or well-being of the study subjects;

(ii) suspend for such period as considered appropriate or cancel the registration issued under rule 17;

(iii) debar its members to oversee any biomedical health research in future for such period as may be considered appropriate.

(2) Where the Ethics Committee or its member, as the case may be, is aggrieved by an order of the authority designated under sub-rule (1), it may, within a period of forty-five working days of the receipt of the order, make an appeal to the Central Government in the Ministry of Health and Family Welfare, and that Government may, after such enquiry, as deemed necessary, and after giving an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case.

CHAPTER V

CLINICAL TRIAL, BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF NEW DRUGS AND INVESTIGATIONAL NEW DRUGS

PART A

CLINICAL TRIAL

19. Clinical trial of new drug or investigational new drug.— (1) No person or institution or organisation shall conduct clinical trial of a new drug or investigational new drug,—

(i) except in accordance with the permission granted by the Central Licencing Authority; and

(ii) without the protocol there of having been approved by the Ethics Committee for clinical trial registered in accordance with the provisions of rule 8.

(2) Every person associated with the conduct of clinical trial of a new drug or investigational new drug shall follow the general principles and practices as specified in the First Schedule.

(3) No person or institution or organisation shall conduct clinical trial of a new drug or investigational new drug except in accordance with the procedure prescribed under the provisions of the Act and these rules.

20. Oversight of clinical trial site.— The work of every clinical trial site shall be overseen by an Ethics Committee for clinical trial registered under rule 8, before initiation and throughout the duration of the conduct of such trial.

21. Application for permission to conduct clinical trial of a new drug or investigational new drug.— (1) Any person or institution or organisation which intends to conduct clinical trial of a new drug or an investigational new drug shall make an application to the Central Licencing Authority duly filled in Form CT-04.

(2) The application made under sub-rule (1) shall be accompanied with the information and documents as specified in the Second Schedule and fee as specified in the Sixth Schedule:

Provided that no fee shall be payable for conduct of a clinical trial by a person of an institution or organisation funded or owned, wholly or partially by the Central Government or by a State Government.

22. Grant of permission to conduct clinical trial.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-04 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant the permission to conduct clinical trial for a new drug or investigational new drug in Form CT-06;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said Authority shall inform the applicant about the deficiencies;

(iii) if not satisfied that the requirements of these rules have been complied with, reject the application, for the reasons to be recorded in writing.

(2) The decision under sub-rule (1) shall be taken within ninety working days.

(3) The applicant, after being informed, as referred to in clause (ii) of sub-rule (1), by the Central Licencing Authority, may,—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in sub-rule (1), and provides required information and documents, the Central Licencing Authority shall scrutinize the application again and if satisfied, grant permission to conduct clinical trial of the new drug or investigational new drug, or if not satisfied, reject the application within a period of ninety days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (3), may file an appeal before the Central Government in the Ministry of Health and Family Welfare within forty-five days from the date of receipt of such decision and the that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

23. Permission to conduct clinical trial of a new drug or investigational new drug as part of discovery, research and manufacture in India.— (1) Notwithstanding anything contained in these rules, where any person or institution or organisation make an application under rule 21 to conduct clinical trial of a new drug or an investigational new drug which is complete as per these rules and fulfills the following conditions, namely:—

(i) the drug is discovered in India; or

(ii) research and development of the drug are being done in India and also the drug is proposed to be manufactured and marketed in India,

such application shall be disposed by way of grant of permission or rejection or processed by way of communication to rectify any deficiency of the application, as the case may be, as specified in rule 22, by the Central Licencing Authority within a period of thirty working days from the date of the receipt of the application by the said authority:

Provided that, where no communication has been received from the Central Licencing Authority to the applicant within the said period, the permission to conduct clinical trial shall be deemed to have been granted by the Central Licencing Authority and such permission shall be deemed to be legally valid for all purposes and the applicant shall be authorised to initiate clinical trial in accordance with these rules.

(2) The applicant who has taken deemed approval under the proviso to sub-rule (1) shall before initiating the clinical trial, inform the Central Licencing Authority in Form CT-4A and the Central Licencing Authority shall on the basis of the said information, take on record the Form CT-4A which shall become part of the official record and shall be called automatic approval of the Central Licencing Authority.

24. Permission to conduct clinical trial of a new drug already approved outside India.— Notwithstanding anything contained in these rules, where any person or institution or organisation makes an application under rule 21 to conduct clinical trial of a new drug which is already approved and marketed in a country, as specified under rule 101,the application, shall be disposed of by way of grant of permission or rejection or processed by way of communication to rectify any deficiency, as the case may be, as specified in rule 22, by the Central Licencing Authority within a period of ninety working days from the date of the receipt of the application by the said Authority.

25. Conditions of permission for conduct of clinical trial.— The permission granted by the Central Licencing Authority to conduct clinical trial under this Chapter shall be subject to following conditions, namely:—

(i) clinical trial at each site shall be initiated after approval of the clinical trial protocol and other related documents by the Ethics Committee of that site, registered with the Central Licencing Authority under rule 8;

(ii) where a clinical trial site does not have its own Ethics Committee, clinical trial at that site may be initiated after obtaining approval of the protocol from the Ethics Committee of another trial site; or an independent Ethics Committee for clinical trial constituted in accordance with the provisions of rule 7:

Provided that the approving Ethics Committee for clinical trial shall in such case be responsible for the study at the trial site or the centre, as the case may be:

Provided further that the approving Ethics Committee and the clinical trial site or the bioavailability and bioequivalence centre, as the case may be, shall be located within the same city or within a radius of 50 kms of the clinical trial site;

(iii) in case an ethics committee of a clinical trial site rejects the approval of the protocol, the details of the same shall be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the clinical trial at the same site;

(iv) the Central Licencing Authority shall be informed about the approval granted by the Ethics Committee within a period of fifteen working days of the grant of such approval;

(v) clinical trial shall be registered with the Clinical Trial Registry of India maintained by the Indian Council of Medical Research before enrolling the first subject for the trial;

(vi) clinical trial shall be conducted in accordance with the approved clinical trial protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and the provisions of these rules;

(vii) status of enrolment of the trial subjects shall be submitted to the Central Licencing Authority on quarterly basis or as appropriate as per the duration of treatment in accordance with the approved clinical trial protocol, whichever is earlier;

(viii) six monthly status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Central Licencing Authority electronically in the SUGAM portal;

(ix) in case of termination of any clinical trial the detailed reasons for such termination shall be communicated to the Central Licencing Authority within thirty working days of such termination;

(x) any report of serious adverse event occurring during clinical trial to a subject of clinical trial, shall, after due analysis, be forwarded to the Central Licencing Authority, the chairperson of the Ethics Committee and the institute where the trial has been conducted within fourteen days of its occurrence as per Table 5 of the Third Schedule and in compliance with the procedures as specified in Chapter VI;

(xi) in case of injury during clinical trial to the subject of such trial, complete medical management and compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty working days of the receipt of order issued by Central Licencing Authority in accordance with the provisions of the said Chapter;

(xii) in case of clinical trial related death or permanent disability of any subject of such trial during the trial, compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty working days of receipt of the order issued by the Central Licencing Authority in accordance with the provisions of the said Chapter;

(xiii) the premises of the sponsor including his representatives and clinical trial sites, shall be open for inspection by officers of the Central Licencing Authority who may be accompanied by officers of the State Licencing Authority or outside experts as authorised by the Central Licencing Authority, to verify compliance of the requirements of these rules and Good Clinical Practices Guidelines, to inspect, search and seize any record, result, document, investigational product, related to clinical trial and furnish reply to query raised by the said officer in relation to clinical trial;

(xiv) where the new drug or investigational new drug is found to be useful in clinical development, the sponsor shall submit an application to the Central Licencing Authority for permission to import or manufacture for sale or for distribution of new drug in India, in accordance with Chapter X of these rules, unless otherwise justified;

(xv) the laboratory owned by any person or a company or any other legal entity and utilised by that person to whom permission for clinical trial has been granted used for research and development, shall be deemed to be registered with the Central Licensing Authority and may be used for test or analysis of any drug for and on behalf of Central Licensing Authority;

(xvi) the Central Licencing Authority may, if considered necessary, impose any other condition in writing with justification, in respect of specific clinical trials, regarding the objective, design, subject population, subject eligibility, assessment, conduct and treatment of such specific clinical trial;

(xvii) the sponsor and the investigator shall maintain the data integrity of the data generated during clinical trial.

26. Validity period of permission to initiate a clinical trial.— The permission to initiate clinical trial granted under rule 22 in Form CT-06 or automatic approval under rule 23 in Form CT 4A shall remain valid for a period of two years from the date of its issue, unless extended by the Central Licencing Authority.

27. Post-trial access of investigational new drug or new drug.— Where any investigator of a clinical trial of investigational new drug or new drug has recommended post-trial access of the said drug after completion of clinical trial to any trial subject and the same has been approved by the Ethics Committee for clinical trial, the post-trial access shall be provided by the sponsor of such clinical trial to the trial subject free of cost,—

(i) if the clinical trial is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and

(ii) the trial subject or legal heir of such subject, as the case may be, has consented

in writing to use post-trial investigational new drug or new drug; and the investigator has certified and the trial subject or his legal heir, as the case may be, has declared in writing that the sponsor shall have no liability for post-trial use of investigational new drug or new drug.

28. Academic clinical trial.— (1) No permission for conducting an academic clinical trial shall be required for any drug from the Central Licencing Authority where,—

(i) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and

(ii) the clinical trial referred to in clause (i) has been initiated after prior approval by the Ethics Committee for clinical trial; and

(iii) the observations generated from such clinical trial are not required to be submitted to the Central Licencing Authority; and

(iv) the observations of such clinical trial are not used for promotional purposes.

(2) In the event of a possible overlap between the academic clinical trial and clinical trial or a doubt on the nature of study, the Ethics Committee concerned shall inform the Central Licencing Authority in writing indicating its views within thirty working days from the receipt of application to that effect.

(3) The Central Licencing Authority shall, after receiving the communication from the Ethics Committee referred to in sub-rule (2), examine it and issue necessary clarification, in writing, within thirty working days from the date of receipt of such communication:

Provided that where the Central Licencing Authority does not send the required communication to such Ethics Committee within thirty working days from the date of receipt of communication from the said Ethics Committee, it shall be presumed that no permission from the Central Licencing Authority is required.

(4) The approved academic clinical trial shall be conducted in accordance with the approved clinical trial protocol, ethical principles specified in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, notified by the Indian Council of Medical Research with a view to ensuring protection of rights, safety and wellbeing of trial subject during conduct of clinical trial of licenced and approved drug or drug formulation for any new indication or new route of administration or new dose or new dosage form for academic research purposes.

29. Inspection of premises relating to clinical trial.— The person or the institution or the organisation permitted to conduct clinical trial under rule 22 in Form CT-06 or rule 23 in Form CT -4A including his representatives and investigator, shall allow any officer authorised by the Central Licencing Authority, who may, if considered necessary, be accompanied by an officer authorised by the State Licencing Authority, to enter the premises and clinical trial site with or without prior notice to inspect, search or seize, any record, statistical result, document, investigational drug and other related material; and reply to queries raised by the inspecting authority in relation to conduct of such clinical trial.

30. Suspension or cancellation of permission to conduct clinical trial.— (1) Where any person or institution or organisation to whom permission has been granted under rule 22 in Form CT-06 or rule 23 in Form CT-4A fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) issue warning in writing describing the deficiency or defect observed during inspection or otherwise, which may affect adversely the right, or well- being of a trial subject or the validity of clinical trial conducted;

(ii) reject the results of clinical trial;

(iii) suspend for such period as considered appropriate or cancel the permission granted under rule 22 in Form CT-06 or rule 23 in Form CT-4A;

(iv) debar the investigator or the sponsor including his representatives to conduct any clinical trial in future for such period as considered appropriate by the Central Licencing Authority.

(2) Where a person or an institution or an organisation to whom permission has been granted under rule 22 in Form CT-06 or rule 23 in Form CT-4A or the sponsor is aggrieved by the order of the Central Licencing Authority, the person or the institution or the organisation may, within a period of sixty working days of the receipt of the order, make an appeal

to the Central Government and that Government may, after such enquiry, as deemed necessary, and after affording an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case. 71

PART B

BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

31. Bioavailability or bioequivalence study of new drug or investigational new drug.— (1) No bioavailability or bioequivalence study of any new drug or investigational new drug shall be conducted in human subjects by any person or institution or organisation except in accordance with the provisions of the Act and these rules.

(2) No person or institution or organisation shall conduct bioavailability or bioequivalence study of a new drug or investigational new drug in human subjects except in accordance with the permission granted by the Central Licencing Authority and without the protocol thereof having been approved by the Ethics Committee registered under rule 8.

(3) Every person associated with the conduct of bioavailability or bioequivalence study of a new drug or investigational new drug shall follow the general principles and practices as specified in the First Schedule.

32. Oversight of bioavailability or bioequivalence study centre.— The work of every bioavailability or bioequivalence study centre shall be overseen by an Ethics Committee registered under rule 8, before initiation and throughout the duration of the conduct of such study.

33. Application for permission to conduct bioavailability or bioequivalence study.— (1) Any person or institution or organisation which intends to conduct bioavailability or bioequivalence study of a new drug or an investigational new drug in human subjects shall obtain permission for conducting bioavailability or bioequivalence study from the Central Licencing Authority by making an application in Form CT-05.

(2) An application for grant of permission to conduct bioavailability or bioequivalence study of any new drug or investigational new drug shall be accompanied by a fee as specified in Sixth Schedule and such other information and documents as specified in the Table 2 of the Fourth Schedule:

Provided that no fee shall be payable for conducting a bioavailability or bioequivalence study by an institution or organisation owned or funded wholly and partially by the Central Government or a State Government.

34. Grant of permission to conduct bioavailability or bioequivalence study.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-05 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant permission to conduct bioavailability or bioequivalence study for a new drug or investigational new drug in Form CT-07; or if not satisfied reject the application, for reasons to be recorded in writing within a period of ninety working days from the date of receipt of the application in Form CT-05;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i).

(2) The decision under sub-rule (1) shall be taken within ninety working days.

(3) The applicant, after being informed as referred to in clause (ii) of sub-rule (1) by the Central Licencing Authority, may,-

(i) rectify the deficiencies within a period specified by the Central Licencing Authority; and

(ii) where the applicant rectifies such deficiencies and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to conduct bioavailability or bioequivalence study of the new drug or investigational new drug; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and resubmission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) and sub-rule (3), may file an appeal before the Central Government within forty-five working days from the date of receipt

of such decision and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

35. Conditions of permission for conduct of bioavailability or bioequivalence study.— The permission granted by the Central Licencing Authority to conduct bioavailability or bioequivalence study under rule 34 shall be subject to following conditions, namely:—

(i) bioavailability or bioequivalence study at each site shall be initiated after approval of bioavailability or bioequivalence study protocol, as the case may be, and other related documents by the Ethics Committee of that site, registered under rule 8;

(ii) where a bioavailability or bioequivalence study centre does not have its own Ethics Committee, bioavailability or bioequivalence study at that site may be initiated after obtaining approval of the protocol from the Ethics Committee registered under rule 8:

Provided that the approving Ethics Committee shall in such case be responsible for the study at the centre:

Provided further that both the approving Ethics Committee and the centre, shall be located within the same city or within a radius of fifty kms of the bioavailability or bioequivalence study centre;

(iii) in case an Ethics Committee of a bioavailability or bioequivalence study centre rejects the approval of the protocol, the details of the same should be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the bioavailability or bioequivalence study at the same site;

(iv) the Central Licencing Authority shall be informed about the approval granted by the registered Ethics Committee within a period of 15 working days of the grant of such approval;

(v) bioavailability or bioequivalence study of new drug or investigational new drug shall be conducted only in the bioavailability or bioequivalence study centre registered with the Central Licencing Authority under rule 47;

(vi) bioavailability or bioequivalence study of investigational new drug shall be registered with the Clinical Trial Registry of India maintained by the Indian Council of Medical Research before enrolling the first subject for the study;

(vii) bioavailability or bioequivalence study shall be conducted in accordance with the approved bioavailability or bioequivalence study protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and provisions of these rules;

(viii) in case of termination of any bioavailability or bioequivalence study, the detailed reasons for such termination shall be communicated to the Central Licencing Authority within thirty working days of such termination;

(ix) any report of serious adverse event occurring during bioavailability or bioequivalence study to a subject of such study, shall, after due analysis, be forwarded to the Central Licencing Authority, the chairperson of the Ethics Committee and the institute or the centre where the bioavailability or bioequivalence study, as the case may be, has been conducted within fourteen days of its occurrence as per Table 5 of the Third Schedule and in compliance with the procedures as specified in Chapter VI;

(x) in case of an injury during bioavailability or bioequivalence study to the subject of such study, complete medical management and compensation shall be provided in accordance with the provisions of Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty days of the receipt of order issued in accordance with the provisions of said Chapter;

(xi) in case of bioavailability or bioequivalence study related death or permanent disability of any subject of such study during the study, compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty days of receipt of the order issued in accordance with the provisions of said Chapter;

(xii) the premises of the sponsor including his representatives and bioavailability and bioequivalence study centre shall be open for inspection by officers of the Central Licencing Authority who may be accompanied by officers of the State Licencing Authority or outside experts as authorised by the Central Licencing Authority, to verify compliance of the requirements of these rules and Good Clinical Practices Guidelines, to inspect, search and seize any record, result, document, investigational product, related to bioavailability or bioequivalence study, as the case may be, and

furnish reply to the queries raised by the said officer in relation to bioavailability or bioequivalence study;

(xiii) the bioavailability or bioequivalence study shall be initiated by enrolling the first subject within a period of one year from the date of grant of permission, failing which prior permission from the Central Licencing Authority shall be required.

36. Validity period of permission to conduct bioavailability or bioequivalence study.— (1) The permission to conduct bioavailability or bioequivalence study granted under rule 34 in Form CT-07 shall remain valid for a period of one year from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity for an extension beyond one year, the said authority may, on the request of the applicant made in writing, extend the period of permission granted for a further period of one year.

37. Inspection of premises relating to bioavailability or bioequivalence study.— The person or the institution or the organisation permitted to conduct bioavailability or bioequivalence study under rule 34 in Form CT-07 including his representatives and investigator, shall allow any officer authorised by the Central Licencing Authority, who may, if considered necessary, be accompanied by an officer authorised by the State Licencing Authority, to enter the premises and bioavailability or bioequivalence study centre with or without prior notice to inspect, search or seize, any record, statistical result, document, investigational drug and other related material and reply to the queries raised by the inspecting authority in relation to conduct of such bioavailability or bioequivalence study.

38. Suspension or cancellation of permission to conduct bioavailability or bioequivalence study.— (1) Where any person or institution or organisation to whom permission has been granted under rule 34 in Form CT-07 fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) issue warning in writing describing the deficiency or defect observed during inspection or otherwise, which may affect adversely the rights, or well- being of a subject enrolled in the study or the validity of bioavailability or bioequivalence study conducted;

(ii) reject the results of bioavailability or bioequivalence study, as the case may be;

(iii) suspend for such period as considered appropriate or cancel the permission granted under rule 34 in Form CT-07;

(iv) debar the investigator or the sponsor including his representatives, to conduct any bioavailability or bioequivalence study in future for such period as considered appropriate by the Central Licencing Authority.

(2) Where a person or an institution or an organisation to whom permission has been granted under rule 34 in Form CT-07or the sponsor is aggrieved by the order of the Central Licencing Authority, the person or the institution or the organisation may, within a period of sixty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary, and after affording an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case within a period of sixty days from the date of receipt of the appeal.

CHAPTER VI

COMPENSATION

39. Compensation in case of injury or death in clinical trial or bioavailability or bioequivalence study of new drug or investigational new drug.— (1) Where any death of a trial subject occurs during a clinical trial or bioavailability or bioequivalence study, the legal heir of the trial subject shall be provided financial compensation by the sponsor or its representative, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, in accordance with the procedure specified in rule 42.

(2) Where permanent disability or any other injury occurs to a trial subject during a clinical trial or bioavailability or bioequivalence study, the trial subject shall be provided financial compensation by the sponsor or its representative, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, in accordance with the procedure specified in rule 42.

(3) The financial compensation referred to in sub-rule (1) or sub-rule (2) shall be in addition to any expenses incurred on medical management of the trial subject.

(4) In the event of an injury, not being permanent in nature, the quantum of compensation shall be commensurate with the loss of wages of the subject as provided in the Seventh Schedule.

(5) The sponsor or its representative shall give an undertaking along with the application for clinical trial permission to the Central Licencing Authority to provide compensation in the case of clinical trial related injury or death for which subjects are entitled to compensation.

(6) Where the sponsor or its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, fails to provide financial compensation, as referred to in sub-rule (1) or sub-rule (2), the Central Licencing Authority shall, after affording an opportunity of being heard, by an order in writing, suspend or cancel the clinical trial or bioavailability or bioequivalence study or restrict the sponsor including its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, to conduct any further clinical trial or bioavailability or bioequivalence study or take any other action for such period as considered appropriate in the light of the facts and circumstances of the case.

40. Medical Management in clinical trial or bioavailability and bioequivalence study of new drug or investigational new drug.— (1) Where an injury occurs to any subject during clinical trial or bioavailability and bioequivalence study of a new drug or an investigational new drug, the sponsor, shall provide free medical management to such subject as long as required as per the opinion of investigator or till such time it is established that the injury is not related to the clinical trial or bioavailability or bioequivalence study, as the case may be, whichever is earlier.

(2) The responsibility for medical management as referred to in sub-rule (1), shall be discharged by the sponsor or the person who has obtained permission from the Central Licencing Authority.

(3) Where the sponsor or its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, fails to provide medical management, as referred to in sub-rule (1), the Central Licencing Authority shall after affording an opportunity of being heard, by an order in writing, suspend or cancel the clinical trial or bioavailability or bioequivalence study or restrict the sponsor including its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, to conduct any further clinical trial or bioavailability or bioequivalence study or take any other action for such period as considered appropriate in the light of the facts and circumstances of the case.

41. Consideration of injury or death or permanent disability to be related to clinical trial or bioavailability and bioequivalence study.— Any injury or death or permanent disability of a trial subject occurring during clinical trial or bioavailability or bioequivalence study due to any of the following reasons shall be considered as clinical trial or bioavailability or bioequivalence study related injury or death or permanent disability, namely:-

(a) adverse effect of the investigational product;

(b) violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator leading to serious adverse event;

(c) failure of investigational product to provide intended therapeutic effect where, the required standard care or rescue medication, though available, was not provided to the subject as per clinical trial protocol;

(d) not providing the required standard care, though available to the subject as per clinical trial protocol in the placebo controlled trial;

(e) adverse effects due to concomitant medication excluding standard care, necessitated as part of the approved protocol;

(f) adverse effect on a child in-utero because of the participation of the parent in the clinical trial;

(g) any clinical trial procedures involved in the study leading to serious adverse event.

42. Procedure for compensation in case of injury or death during clinical trial, bioavailability and bioequivalence study.— (1) The investigator shall report all serious adverse events to the Central Licencing Authority, the sponsor or its representative, who has obtained permission from the Central Licencing Authority for conduct of clinical trial or bioavailability or bioequivalence study, as the case may be, and the Ethics Committee that accorded approval to the study protocol, within twenty-four hours of their occurrence; and if the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reasons for delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

(2) A case of serious adverse event of death shall be examined in the following manner, namely:-

(i) the Central Licencing Authority shall constitute an independent expert committee to examine the cases and make its recommendations to the said authority for arriving at the cause of death and quantum of compensation in case of clinical trial related death;

(ii) the sponsor or its representative and the investigator shall forward their reports on serious adverse event of death after due analysis to the Central Licencing Authority and the head of the institution where the clinical trial or bioavailability or bioequivalence study has been conducted within fourteen days of the knowledge of occurrence of serious adverse event of death;

(iii) the Ethics Committee for clinical trial shall forward its report on serious adverse event of death after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the said sponsor or its representative, who has obtained permission from the Central Licencing Authority for conduct of clinical trial or bioavailability or bioequivalence study, as the case may be, to the Central Licencing Authority within a period of thirty days of receiving the report of the serious adverse event of death from the investigator;

(iv) the Central Licencing Authority shall forward the report of the investigator, sponsor or its representative and the Ethics Committee to the Chairperson of the expert committee;

(v) the expert committee shall examine the report of serious adverse event of death and make its recommendations available to the Central Licencing Authority for the purpose of arriving at the cause of the serious adverse event of death within sixty days from the receipt of the report of the serious adverse event, and the expert committee while examining the event, may take into consideration, the reports of the investigator, sponsor or its representative and the Ethics Committee for clinical trial;

(vi) in case of clinical trial or the bioavailability or bioequivalence study related death, the expert committee shall also recommend the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or his representative who has obtained the permission to conduct the clinical trial or the bioavailability or bioequivalence study, as the case may be;

(vii) the Central Licencing Authority shall consider the recommendations of the expert committee and shall determine the cause of death with regards to the relatedness of the death to the clinical trial or the bioavailability or bioequivalence study, as the case may be;

(viii) in case of clinical trial or the bioavailability or bioequivalence study related death, the Central Licencing Authority shall, after considering the recommendations of the expert committee, by order, decide the quantum of compensation, determined as per the formula specified in the Seventh Schedule, to be paid by the sponsor or its representative and shall pass orders as deemed necessary within ninety days of the receipt of the report of the serious adverse event;

(ix) the sponsor or its representative shall pay the compensation in case the serious adverse event of death is related to clinical trial or the bioavailability or bioequivalence study, as specified in the order referred to in clause (viii) of the Central Licencing Authority within thirty days of the receipt of such order.

(3) Cases of serious adverse events of permanent disability or any other injury other than deaths shall be examined in the following manner, namely:—

(i) the sponsor or its representative, and the Investigator shall forward their reports on serious adverse event, after due analysis, to the Central Licencing Authority, chairperson of the Ethics Committee for clinical trial and head of the institution where the trial or bioavailability or bioequivalence study has been conducted within fourteen days of the reporting of serious adverse event;

(ii) the Ethics Committee for clinical trial shall forward its report on serious adverse event of permanent disability or any other injury other than deaths, as the case may be, after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or its representative who has obtained permission to conduct clinical trial or the bioavailability or bioequivalence study, as the case may be, within thirty days of receiving the report of the serious adverse event;

(iii) the Central Licencing Authority shall determine the cause of the injury and pass order as specified in clause (iv), or may constitute an independent expert committee, wherever it considers necessary, to examine such serious adverse events of injury, and such independent expert committee shall recommend to the Central Licencing Authority for the purpose to arrive at the cause of the serious adverse event and also the quantum of compensation, as determined in accordance with formula as specified in the Seventh Schedule in case of clinical trial or bioavailability or bioequivalence study related injury, within a period of sixty days of receipt of the report of the serious adverse event;

(iv) in case of clinical trial or the bioavailability or bioequivalence study related injury, the Central Licencing Authority shall, by order, decide the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or his representative who has obtained the

permission to conduct the clinical trial or the bioavailability or bioequivalence study, as the case may be, within a period of ninety days of receipt of the report of the serious adverse event;

(v) the sponsor or its representative, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, as the case may be, shall pay the compensation in case of clinical trial or bioavailability or bioequivalence study related injury, as specified in the order of the Central Licencing Authority referred to in clause (iv) within thirty days of receipt of such order.

43. Medical management and compensation for injury or death relating to biomedical and health research overseen by an Ethics Committee for biomedical and health research as referred to in Chapter IV.— Notwithstanding anything contained in these rules, medical management and compensation for injury or death relating to biomedical and health research, overseen by an Ethics Committee for clinical trials as referred to in Chapter IV, shall be in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants specified by the Indian Council of Medical Research from time to time.

CHAPTER VII

BIOAVAILABILITY AND BIOEQUIVALENCE STUDY CENTRE

44. Registration of bioavailability and bioequivalence study centre.— No bioavailability and bioequivalence study centre shall conduct any bioavailability study or bioequivalence study of a new drug or investigational new drug in human subjects except in accordance with the registration granted by the Central Licencing Authority under these rules.

45. Application for registration of bioavailability and bioequivalence study centre.— (1) Application for registration of any bioavailability and bioequivalence study centre with the Central Licencing Authority shall be made to the said authority in Form CT-08.

(2) The application under sub-rule (1) shall be accompanied by a fee as specified in the Sixth Schedule and such other information and documents as specified in the Fourth Schedule.

46. Inspection of bioavailability and bioequivalence study centre.— On receipt of an application under sub-rule (1) of rule 45, any officer authorised by the Central Licencing Authority who may be accompanied by the officers authorised by the State Licencing Authority, may cause an inspection of the bioavailability and bioequivalence study centre to verify the facility of the centre and the capacity of the applicant to comply with the requirements of these rules.

47. Grant of registration to bioavailability and bioequivalence study centre.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-08 and such further enquiry, if any, as may be considered necessary, and if satisfied, that the requirements of these rules have been complied with, grant registration to the applicant in Form CT-09 within a period of ninety working days from the date of receipt of its application in Form CT-08; or if not satisfied, reject the application, for reasons to be recorded in writing, from the date the application was made under sub-rule (1) of rule 45;

(2) In case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same are to be rectified, said authority shall inform the applicant of the deficiencies within the period as provided in sub-rule (1);

(3) The applicant may, after being informed by the Central Licencing Authority as specified in sub-rule(2),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority; and

(ii) where the applicant rectifies the deficiency within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant registration to the applicant in Form CT-09 or if not satisfied, reject the application within a period of ninety days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (3), may file an appeal within forty-five days from the date of receipt of such rejection before the Central Government and that Government may, after such enquiry and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty days.

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48. Validity period and renewal of registration of bioavailability and bioequivalence centre.— (1) The registration granted under rule 47 in Form CT-09 shall remain valid for a period of five years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2)The bioavailability or bioequivalence centre shall make an application for renewal of registration in Form CT-08 along with documents as specified in the Fourth Schedule at least ninety days prior to date of expiry of its registration:

Provided that if the application for renewal of registration is received by the Central Licencing Authority ninety days prior to date of expiry, the registration shall continue to be in force until orders are passed by the said authority on the application.

(3)The Central Licencing Authority shall, after scrutiny of information enclosed with the application and after taking into account the inspection report, and such further enquiry, if any, as may be considered necessary, if satisfied, that the requirements of these rules,—

(i) have been complied with, grant registration or renew registration in Form CT-09;

(ii) have not been complied with, reject the application, for reasons to be recorded in writing, within a period of forty-five days, from the date the application was made under sub-rule (2).

49. Conditions of registration.— The registration granted under rule 47 in Form CT-09 shall be subject to following conditions, namely:—

(i) the centre shall maintain the facilities and adequately qualified and trained personnel as specified in the Fourth Schedule for performing its functions;

(ii) the centre shall initiate any bioavailability study or bioequivalence study of any new drug or investigational new drug in human subjects after approval of the protocol and other related documents by the Ethics Committee for clinical trial and permission of such study granted by the Central Licencing Authority;

(iii) where the bioavailability or bioequivalence study centre does not have its own Ethics Committee, bioavailability or bioequivalence study at that site may be initiated after obtaining approval of the protocol from another Ethics Committee for clinical trial registered under rule 8:

Provided that the approving Ethics Committee accepts the responsibility for the study at the centre and, both the approving Ethics Committee and the centre, are located within the same city or within a radius of fifty kms of the centre;

(iv) the Central Licencing Authority shall be informed about the approval of the Ethics Committee for clinical trial;

(v) bioavailability or bioequivalence study of investigational new drug shall be registered with the Clinical Trial Registry of India before enrolling the first subject for the study;

(vi) study shall be conducted in accordance with the approved protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and provisions of the Act and these rules;

(vii) in case of termination of any such study prematurely, the detailed reasons for such termination shall be communicated to the Central Licencing Authority immediately;

(viii) any report of serious adverse event occurring during study to the subject of such study shall, after due analysis, be forwarded to Central Licencing Authority within fourteen days of its occurrence in the format as specified in Table 5 of the Third Schedule and in compliance with the procedures as specified in rule 42;

(ix) in case of an injury to the study subject during study, the complete medical management and compensation in the case of study related injury shall be provided in accordance with the provisions of Chapter VI and details of compensation paid to the trial subject in such cases shall be intimated to the Central Licencing Authority within thirty days of receipt of the order;

(x) in case of death, permanent disability, injury other than death and permanent disability, as the case may be, of a study subject, compensation shall be provided in accordance with the provisions of Chapter VI and details of compensation paid to the trial subject or his legal heir, as the case may be, in such cases shall be intimated to the Central Licencing Authority within thirty days of receipt of the order;

(xi) if there is any change in constitution or ownership of the bioavailability and bioequivalence study centre, the centre shall intimate about the change in writing to the Central Licencing Authority within thirty days of such change;

(xii) the study centre shall maintain data, records, and other documents related to the conduct of the bioavailability or bioequivalence study for a period of five years after completion of such study or for at least two years after the expiration date of the batch of the new drug or investigational new drug studied, whichever is later;

(xiii) the bioavailability and bioequivalence study centre shall allow any officer authorized by the Central Licencing Authority who may be accompanied by an officer authorised by State Licencing Authority to enter the premises with or without prior notice, to inspect any record, statistical observation or results or any documents related to bioavailability study and bio-equivalence study and furnish information to the queries raised by such authorised person, in relation to the conduct of the said study;

(xiv) the Central Licencing Authority may, if considered necessary, impose additional condition, in writing with justification, in respect of specific bioavailability and bioequivalence study regarding the objective, design, subject population, subject eligibility, assessments, conduct and treatment of such specific study.

50. Inspection of bioequivalence and bioavailability study centre registered with Central Licencing Authority.— The bioavailability and bioequivalence study centre registered by the Central Licencing Authority under Rule 47 in Form CT-09, including his representatives and investigator, shall allow any officer authorised by the Central Licencing Authority, who may be accompanied by an officer authorised by the State Licencing Authority, to enter the premises of the bioavailability and bioequivalence study centre with or without prior consent, to inspect, search or seize, any record, document, investigational product and other related material and reply to queries raised by the inspecting authority in relation to functioning of the centre.

51. Suspension or cancellation of registration of bioavailability and bioequivalence study centre.— (1) Where any bioavailability and bioequivalence study centre including his representatives or investigator, fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(a) issue warning in writing describing the deficiency or defect observed during inspection or otherwise, which may affect adversely the right or well-being of trial subject or the validity of any study conducted;

(b) reject the results of the study;

(c) suspend the conduct of a study;

(d) suspend for such period as considered appropriate or cancel the registration granted under rule 47 in Form CT-09; and

(e) debar the centre including its representatives to conduct any bioavailability and bioequivalence study in future for such period as considered appropriate by the Central Licencing Authority.

(2) Where a bioavailability and bioequivalence study centre registered under Form CT-

09 against whom an order has been made under sub-rule (1) is aggrieved by the order of the Central Licencing Authority, the bioavailability and bioequivalence study centre may within a period of sixty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as may be considered appropriate in the facts and circumstances of the case.

CHAPTER VIII

MANUFACTURE OF NEW DRUGS OR INVESTIGATIONAL NEW DRUGS FOR CLINICAL TRIAL, BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

52. Application for permission to manufacture of new drug or investigational new drug for clinical trial or bioavailability and bioequivalence study or for examination, test and analysis. –

(1) No person shall manufacture a new drug or an investigational new drug to conduct clinical trial or bioavailability or bioequivalence study or for examination, test and analysis without obtaining permission to manufacture such new drug or investigational new drug from the Central Licencing Authority.

(2) Any person who intends to manufacture a new drug or an investigational new drug to conduct clinical trial or bioavailability and bioequivalence study or for examination, test and analysis shall make an application in Form CT-10 to the Central Licencing Authority to obtain the permission referred to in sub-rule(1).

(3) The application referred in sub-rule (2) shall be accompanied with such documents and information as specified in the Fourth Schedule along with fee as specified in the Sixth Schedule.

53. Grant of permission to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study, or for examination, test and analysis.— (1)The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-10 and such further enquiry, if any, as may be considered necessary, if satisfied, that the requirements of these rules have been complied with, grant permission to manufacture the new drug or investigational new drug for conduct of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis, as the case may be, the new drug or investigational new drug, in Form CT-11 within a period of ninety working days from the date of receipt of its application in Form CT-10; or if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety working days from the date the application was made under sub-rule (2) of rule 52.

(2)In case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said authority shall inform the applicant of the deficiencies within the period specified in sub-rule (1)

(3) The applicant may, after being informed by the Central Licencing Authority as specified in sub-rule (2),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority; and

(ii) where the applicant rectifies the deficiency within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to manufacture for conduct of clinical trial or bioavailability or bioequivalence study, or for examination, test and analysis, as the case may be, for the new drug or investigational new drug; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (3), may file an appeal before the Central Government within forty-five days from the date of receipt of such decision and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty days from the date of filing the appeal.

54. Validity period of permission to manufacture of new drug or investigational new drugs for clinical trial or bioavailability and bioequivalence study, or for examination, test and analysis.— (1) The permission granted under rule 53 in Form CT-11 shall remain valid for a period of three years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity and exigency, it may, on the request of the applicant made in writing, by order, and for reasons to be recorded, extend the period of the permission granted for a further period of one year.

55. Condition of permission.— The grant of permission under rule 53 in Form CT-11 shall be subject to the following conditions, namely:—

(i) the permission holder shall make use of new drug manufactured under Form CT-11 only for the purposes of conducting clinical trial or bioavailability and bioequivalence study or for examination, test and analysis and no part of it shall be sold in the market or supplied to any other person or agency or institution or organisation;

(ii) the permission holder shall manufacture new drugs for the purposes of clinical trial or bioavailability and bioequivalence study or for examination, test and analysis in small quantities in accordance with the provisions of these rules and at places specified in the permission and in accordance with the principles of Good Manufacturing Practices;

(iii) the permission holder shall keep a record of new drugs manufactured and persons to whom the drugs have been supplied for clinical trial or bioavailability and bioequivalence study or for examination, test and analysis;

(iv) where new drug manufactured for purposes of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis is left over or remains unused or gets damaged or its specified shelf life has expired or has been found to be of sub- standard quality, the same shall be destroyed and action taken in respect thereof shall be recorded.

56. Licence to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under rule 53, the person, who intends to manufacture the new drug or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis of new drugs or investigational new drugs, shall make an application for grant of licence to manufacture new drug or investigational new drugs in accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission under rule 53 in Form CT-11 obtained by the applicant from the Central Licencing Authority to manufacture the new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.

57. Inspection of new drugs or investigational new drugs manufactured for clinical trial or bioavailability and bioequivalence study or for examination, test and analysis.— The permission holder or the person, to whom new drugs have been supplied for conducting clinical trial or bioavailability and bioequivalence study or for examination, test and analysis, shall allow any officer authorised by the Central Licencing Authority or the State Licencing Authority to enter, the premises where the new drug is being manufactured or stored, with or without prior notice, to inspect such premises and records, investigate the manner in which the drugs are being manufactured or stored or used and to take sample thereof.

58. Suspension or cancellation of manufacturing permission for new drug or investigational new drugs.— (1) Subject to provisions of rule 55, where the permission holder, fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving that person an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) suspend the permission for such period as considered appropriate;

(ii) cancel the permission granted under rule 53 in Form CT-11.

(2) Where the permission holder whose permission has been suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, he may, within sixty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case.

59. Application for permission to manufacture unapproved active pharmaceutical ingredient for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.—

(1) Where a manufacturer of a pharmaceutical formulation intends to procure active pharmaceutical ingredient, which is not approved under rule 76 or rule 81, for development of formulation and to manufacture batches for test or analysis or clinical trial or bioavailability and bioequivalence study of such formulation, the application for permission to manufacture such drug shall be made to the Central Licencing Authority by the manufacturer of pharmaceutical formulation in Form CT-12 and manufacturer of the active pharmaceutical ingredient in Form CT-13**.**

(2) The application under sub-rule (1) shall be accompanied by such other particulars and documents as are specified in Form CT-12 or Form CT-13, as the case maybe.

60. Grant of permission to manufacture unapproved active pharmaceutical ingredient for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application under rule 59 in Form CT-12 or CT-13, as the case may be, and such further enquiry, if any, as may be considered necessary:—

(i) if satisfied, that the requirements of these rules have been complied with, grant the permission to the manufacturer of active pharmaceutical ingredient in Form CT-15 to manufacture the unapproved active pharmaceutical ingredient and to the manufacturer of pharmaceutical formulation in Form CT-14 for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study within ninety working days; or

(ii) if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety working days, from the date, the application was made under sub-rule (1) of rule 59; or

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(iii) if the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i).

(2) The applicant may, after being informed, by the Central Licencing Authority as referred to in clause (iii) of sub-rule (1),-

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in sub-rule (1), within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to the manufacturer of active pharmaceutical ingredient in Form CT-15 to manufacture the unapproved active pharmaceutical ingredient and to the manufacturer of pharmaceutical formulation in Form CT-14 for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (2), may file an appeal before the Central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty days from the date of filing the appeal.

61. Validity period of the permission to manufacture unapproved active pharmaceutical ingredient and its formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— (1) The permission granted under rule 60 in Form CT-14 or Form CT-15, as the case may be, shall remain valid for a period of three years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity and exigency, it may, on the request of the applicant made in writing, by order and for reasons to be recorded extend the period of permission granted for a further period of one year.

62. Suspension or cancellation of permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— (1) Subject to provision of rule 60, where the formulation manufacturer or an active pharmaceutical ingredient manufacturer fails to comply with any provisions of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) suspend the permission for such period as considered appropriate;

(ii) cancel the permission granted under rule 60 in Form CT-14 or Form CT-15.

(2) Where the formulation manufacturer or active pharmaceutical ingredient manufacturer whose permission has been suspended or cancelled under sub-rule (1), is aggrieved by an order of the Central Licencing Authority, such manufacturer may, within forty-five days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as may be considered appropriate in the facts and circumstances of the case.

63. Conditions of permission.— The permission granted under rule 60 in Form CT-14 or Form CT-15 shall be subject to following conditions, namely:—

(i) the manufacturer of pharmaceutical formulation or the active pharmaceutical ingredient shall make use of the unapproved active pharmaceutical ingredient manufactured on the basis of permission issued under rule 60, only for the purposes specified in the said permission, and no part of it shall be sold in the market;

(ii) the permission holder shall manufacture such active pharmaceutical ingredient or its pharmaceutical formulation for the purposes as specified in permission in accordance with the provisions of these rules and at places referred to in such permission and, in case, the manufacture of such drugs is for clinical trial or bioavailability and bioequivalence study, it should be manufactured in accordance with the principles of Good Manufacturing Practices;

(iii) the manufacturer of a pharmaceutical formulation and active pharmaceutical ingredient referred to in clause (i), shall keep all necessary records to indicate the quantity of drug procured, manufactured, used, disposed of in any manner and other matters related thereto;

(iv) where unapproved active pharmaceutical ingredient and pharmaceutical formulation manufactured in accordance with the permission issued under rule 60 is left over or remains, unused or gets damaged or its shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed and action taken in respect thereof shall be recorded.

64. Licence to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability and bioequivalence study under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under rule 60, the person intending to manufacture unapproved active pharmaceutical ingredient or pharmaceutical formulation of the new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis, shall make an application for grant of licence to manufacture unapproved active pharmaceutical ingredient or pharmaceutical formulation for test or analysis or clinical trial or bioavailability in accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission granted under rule 60 in Form CT-14 or Form CT-15, as the case may be, obtained by the applicant from the Central Licencing Authority to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study.

65. Inspection of manufacturer of unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— The manufacturer of active pharmaceutical ingredient or formulation, referred to in rule 60, shall allow any officer authorised by the Central Licencing Authority or the person authorised by the State Licencing Authority to enter the premises where the unapproved active pharmaceutical ingredient is being manufactured, stored and used, with or without prior notice, to inspect such premises and records, inspect the manner in which the unapproved active pharmaceutical ingredient is being manufactured and stored or used and to take sample thereof.

66. Manner of labelling.— (1) Any new drug or investigational new drug manufactured, for the purpose of clinical trial or bioavailability or bioequivalence study, shall be kept in containers bearing labels, indicating the name of the drug or code number, batch or lot number, wherever applicable, date of manufacture, use before date, storage conditions, name of the institution or organisation or the centre where the clinical trial or bioavailability or bioequivalence study is proposed to be conducted, name and address of the manufacturer, and the purpose for which it has been manufactured.

(2) Where a new drug or an investigational new drug is manufactured by the permission holder on behalf of another person, the permission holder shall indicate on the label of the container of such drug, the name and address of the manufacturer and the person to whom it is being supplied along with the scientific name of such drug, if known, or the reference which shall enable such drug to be identified and the purpose for which it is manufactured.

(3) No person or manufacturer shall alter, obliterate or deface any inscription or mark made on the container, label or wrapper of any new drug manufactured without permission of the Central Licencing Authority.

CHAPTER IX

IMPORT OF NEW DRUGS AND INVESTIGATIONAL NEW DRUGS FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALANCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

67. Application for import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) No person shall import a new drug or any substance relating thereto for conducting clinical trial or bioavailability or bioequivalence study or for examination, test and analysis except in accordance with the licence granted by Central Licencing Authority.

(2) Any person or institution or organisation who intends to import a new drug or any substance relating thereto for conducting clinical trial or bioavailability or bioequivalence study or for examination, test and analysis shall make an application in Form CT-16 to the Central Licencing Authority.

(3) The application under sub-rule (2) shall be accompanied by a fees specified in the Sixth Schedule and such other information and documents as specified in Form CT-16.

68. Grant of licence for import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-16 and such further enquiry, if any, as may be considered necessary,—

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(i) if satisfied, that the requirements of these rules have been complied with, grant the licence to import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis in Form CT-17 within a period of ninety days from the date of receipt of its application in FormCT-16;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i);

(iii) if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety days, from the date of the application made under sub-rule (2) of rule 67;

(2) The applicant may, after being informed, by the Central Licencing Authority as referred to in clause (ii) of sub-rule (1),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant licence to import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (2), may file an appeal before the Central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

69. Validity period of licence for import of new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) The licence granted under rule 68 in Form CT-17 shall remain valid for a period of three years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity and exigency, it may, on the request of the applicant made in writing, extend the period of the licence granted under rule 68 for a further period of one year.

70. Condition of licence.— The licence granted under rule 68 in Form CT-17 is subject to the following conditions, namely:—

(i) it shall be the responsibility of the licencee to ensure that the new drug has been manufactured in accordance with the provisions of the Act, these rules and principles of Good Manufacturing Practices;

(ii) the licencee shall make use of a new drug or substance relating thereto imported on the basis of licence granted under rule 68 in Form CT-17 only for the purposes of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis and no part of such new drug or substance relating thereto shall be sold in the market or supplied to any other person or agency or institution or organisation;

(iii) the licencee shall maintain records of imported new drug or substance relating thereto to indicate the quantity of drug imported, used, disposed of in any manner and other matters related thereto;

(iv) where the imported new drug or substance relating thereto is left over or remains unused or gets damaged or its specified shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed and details of action taken in such cases shall be recorded.

71. Inspection of imported new drug for clinical trial or the bioavailability or bioequivalence study or for examination, test and analysis.— The person licenced to import a new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis shall allow any officer authorised by the Central Licencing Authority to enter the premises where a new drug or substances relating thereto has been manufactured or imported, is stocked or is being used, with or without prior notice, to inspect such premises and records, investigate the manner in which such drug is being stocked or used or to take sample thereof if so required by the Central Licencing Authority or his authorised person.

72. Suspension or cancellation of import licence of new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) Where the person to whom a licence has been granted under rule 68, fails to comply with any provisions of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, suspend or cancel the licence for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates and direct the imported new drugs to be disposed of in the manner specified in the said order.

(2) Where the person whose licence has been suspended or cancelled under sub-rule (1), is aggrieved by an order of the Central Licencing Authority, such person may, within a period of forty-five days of the receipt of the order of suspension or cancellation, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such order in relation thereto as considered appropriate within a period of sixty working days from the date of filing the appeal.

73. Manner of labelling.— (1) Any new drugs or investigational new drugs imported for the purpose of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis shall be kept in containers bearing labels, indicating the name of the drug or code number, batch or lot number, wherever applicable, date of manufacture, use before date, storage conditions, name of the institution or organisation or the centre where the clinical trial or bioavailability or bioequivalence study or for examination, test and analysis is proposed to be conducted, name and address of the manufacturer, and the purpose for which it has been imported.

(2) Where a new drug or an investigational new drug is imported by the licencee on behalf of another person, the licencee shall indicate on the label of the container of the such drug, the name and address of the importer and the person to whom it is being supplied along with the scientific name of such drug, if known, or the reference which shall enable such drug to be identified and the purpose for which it is manufactured.

(3) No person or importer shall alter, obliterate or deface any inscription or mark made on the container, label or wrapper of any new drug imported without permission of the Central Licencing Authority.

CHAPTER X

IMPORT OR MANUFACTURE OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

74. Regulation of new drug.— No person shall import or manufacture for sale or for distribution any new drug in the form of active pharmaceutical ingredient or pharmaceutical formulation, as the case may be, except in accordance with the provisions of the Act and these rules.

75. Application for permission to import new drug for sale or distribution.— (1) Any person who intends to import new drug in the form of active pharmaceutical ingredient or pharmaceutical formulation, as the case may be, for sale or for distribution in India, shall make an application to obtain a permission from the Central Licencing Authority in Form CT-18 along with a fee as specified in the Sixth Schedule:

Provided that an application for grant of permission to import a new drug, in the form of active pharmaceutical ingredient which is a new drug not approved earlier, shall be accompanied by an application for grant of permission to manufacture pharmaceutical formulation of that new drug.

(2) Where a new drug proposed to be marketed by any person is a new drug having unapproved new molecule, the application in Form CT-18 shall be accompanied by data and other particulars including result of local clinical trial as specified in the Second Schedule along with data specified in Table 1 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(3) Where a new drug is proposed to be marketed which has been approved as a new drug in the country, the application in Form CT-18 shall be accompanied by data and other particulars as specified in the Second Schedule along with data specified in Table 2 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(4) Where a new drug which is already permitted for certain claims, is now proposed to be marketed by any person for new claims, new indication or new dosage form or new route of administration or new strength, application in Form CT-18 shall be accompanied by data and other particulars including result of local clinical trial as specified in the Second Schedule along with data specified in Table 3 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(5) In case a new drug which is a fixed dose combination, the application in CT-18 shall be accompanied by data and other particulars including result of local clinical trial as the case may be, as specified in the Second Schedule along with data specified in Table 1 or Table 2 or Table 3, as the case may be, of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(6) A person intends to market phyto-pharmaceutical drugs shall make an application in CT-18 to the Central Licencing Authority along with data specified in Table 4 of the Second Schedule and it shall be accompanied with a fee as specified in the Sixth Schedule.

(7) The local clinical trial may not be required to be submitted along with the application referred to in sub-rule (1) if,—

(i) the new drug is approved and marketed in countries specified by the Central Licencing Authority under rule 101 and if no major unexpected serious adverse events have been reported; or

(ii) the application is for import of a new drug for which the Central Licencing Authority had already granted permission to conduct a global clinical trial which is ongoing in India and in the meantime such new drug has been approved for marketing in a country specified under rule 101; and

(iii) there is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug; and

(iv) the applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the Central Licencing Authority:

Provided that the Central Licencing Authority may relax this condition, where the drug is indicated in life threatening or serious diseases or diseases of special relevance to Indian health scenario or for a condition which is unmet need in India such as XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, HIV, or for the rare diseases for which drugs are not available or available at a high cost or if it is an orphan drug.

(8) The submission of requirements relating to animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and carcinogenicity in the application referred to in sub-rule (1), may be modified or relaxed in case of new drugs approved and marketed for more than two years in other countries, if the Central Licencing Authority is satisfied that there is adequate published evidence regarding the safety of the drug, subject to other provisions of these rules.

76. Grant of permission for import of new drugs for sale or distribution.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-18 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant the permission to import new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-19 or pharmaceutical formulation for sale or for distribution in Form CT-20, as the case may be, within a period of ninety working days from the date of receipt of its application in Form CT-18;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i);

(iii) if not satisfied that the requirements of these rules have been complied with, reject the application, for that reasons to be recorded in writing, within a period of ninety working days, from the date of the application made under rule 75.

(2) The applicant may, after being informed by the Central Licencing Authority as referred to in clause (ii) of sub-rule (1),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in clause (i), within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to import new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-19 or pharmaceutical formulation for sale or for distribution in Form CT-20, as the case may be; or if not satisfied, reject the application within a period of ninety days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) and sub-rule (2), may file an appeal before the Central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days from the date of filing the appeal.

77. Condition of permission for import of new drugs for sale or distribution.— The permission for import of new drugs for sale or for distribution under rule 76 shall be subject to the following conditions, namely:—

(i) the new drugs shall conform to the specifications approved by the Central Licencing Authority;

(ii) the labeling of the drugs shall conform to the requirements specified in the Drugs and Cosmetics Rules, 1945;

(iii) the label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning: "WARNING: To be sold by retail on the prescription of a ……only" which shall be in red box;

(iv) as post marketing surveillance, the applicant shall submit Periodic Safety Update Reports as specified in the Fifth Schedule;

(v) all reported adverse reactions related to drug shall be intimated to the Central Licencing Authority and regulatory action resulting from their review shall be complied with;

(vi) no claims except those mentioned above shall be made for the drug without prior approval of the Central Licencing Authority;

(vii) specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Central Licencing Authority before the drugs is marketed;

(viii) in case of import, each consignment shall be accompanied by a test or analysis report;

(ix) if long-term stability data submitted do not cover the proposed shelf-life of the product, the stability study shall be continued to firmly establish the shelf-life and the complete stability data shall be submitted.

78. Suspension or cancellation of import permission for new drug.— (1) Where the importer fails to comply with any provision of the Act and these Rules, the Central Licencing Authority may, after giving show cause notice and an opportunity of being heard, by an order in writing, may suspend the permission for such period as considered appropriate or cancel the permission.

(2) Where the importer whose permission has been suspended or cancelled under sub-rule (1), is aggrieved by an order of the Central Licencing Authority, such importer may, within forty-five days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after giving an opportunity of being heard, pass such order as may be considered appropriate in the facts and circumstances of the case.

79. Licence to import new drug for sale or for distribution under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under Rule 76, the person intending to import new drug for sale shall make an application to the Central Licencing Authority as per provisions of the Drugs and Cosmetics Rules, 1945 to obtain a licence for import of new drug for sale or for distribution.

(2) The application referred in sub-rule (1) shall be accompanied by the permission in Form CT-19 or Form CT-20, as the case may be, obtained by the applicant from the Central Licencing Authority to import the new drugs.

80. Application for permission to manufacture new drug for sale or distribution.— (1) A person who intends to manufacture new drug in the form of active pharmaceutical ingredient or pharmaceutical formulation, as the case may be, for sale or distribution, shall make an application for grant of permission to the Central Licencing Authority in Form CT-21 along with a fee as specified in the Sixth Schedule:

Provided that no fee shall be required to be paid along with the application for manufacture of a new drug based on successful completion of clinical trials from Phase I to Phase III under these Rules in India, where fee has already been paid by the same applicant for conduct of such clinical trials:

Provided further that an application for grant of permission to manufacture a new drug for sale or distribution in the form of active pharmaceutical ingredient having a new drug molecule not approved earlier shall be accompanied by an application for grant of permission to manufacture for sale or distribution of pharmaceutical formulation of the said new drug.

(2) Where a new drug, proposed to be manufactured, is a new drug having unapproved new molecule, the application in Form CT-21 shall be accompanied by data and other particulars including results of local clinical trial as specified in the Second Schedule along with data specified in Table 1 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(3) Where a new drug, proposed to be manufactured which has been approved as a new drug, the application in Form CT-21 shall be accompanied by data and other particulars as specified in the Second Schedule

along with data specified in Table 2 of the Second Schedule and accompanied with fee as specified in Sixth Schedule.

(4) Where a new drug which is already permitted for certain claims, is now proposed to be manufactured for new claims, namely new indication or new dosage form or new route of administration or new strength, application in Form CT-21 shall be accompanied by data and other particulars including results of local clinical trial as specified in the Second Schedule along with data specified in Table 3 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(5) In case of a new drug which is a fixed dose combination, the application in Form CT-21 shall be accompanied by data and other particulars including results of local clinical trial as specified in the Second Schedule along with data specified in Table 1 or Table 2 or Table 3, as the case may be, of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(6) A person who intends to market phyto -pharmaceutical drugs shall make an application in Form CT-21 to the Central Licencing Authority along with data specified in Table 4 of Second Schedule and it shall be accompanied with a fee as specified in the Sixth Schedule.

(7) The local clinical trial may not be required to be submitted along with the application referred to in sub-rule (1) if,-

(i) the new drug is approved and marketed in countries specified by the Central Licencing Authority under rule101 and if no major unexpected serious adverse events have been reported; or

(ii) there is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug; and

(iii) the applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the Central Licencing Authority:

Provided that the Central Licencing Authority may relax this condition, where the drug is indicated in life threatening or serious diseases or diseases of special relevance to Indian health scenario or for a condition which is unmet need in India such as XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, HIV, or for the rare diseases for which drugs are not available or available at a high cost or if it is an orphan drug.

(8) In the application referred to in sub-rule (1), the submission of requirements relating to animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries, if the Central Licencing Authority is satisfied that there is adequate published evidence regarding the safety of the drug, subject to other provisions of these rules.

81. Grant of permission for manufacture of new drug for sale or distribution.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-21 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant permission to manufacture new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-22 or pharmaceutical formulation for sale or for distribution in Form CT-23, as the case may be, within a period of ninety working days from the date of receipt of its application in Form CT-21;

(ii) if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety working days, from the date, the application made under rule 80; and

(iii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i).

(2) The applicant may, after being informed by the Central Licencing Authority as referred to in clause (iii) of sub-rule (1),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to manufacture new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-22 or pharmaceutical formulation for sale or for

distribution in Form CT-23, as the case may be; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (2), may file an appeal before the central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days from the date of filing the appeal.

82. Condition of permission for manufacture of new drugs for sale or distribution.— The permission granted under rule 81 in Form CT-22 or in Form CT-23 shall be subject to following conditions, namely:—

(i) the new drugs shall conform to the specifications approved by the Central Licencing Authority;

(ii) the labeling of the drugs shall conform to the requirements specified in the Drugs and Cosmetics Rules, 1945;

(iii) the label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING: To be sold by retail on the prescription of a_____ Only" and it shall be in box with red back ground.

(iv) as post marketing surveillance, the applicant shall submit Periodic Safety Update Reports as specified in the Fifth Schedule;

(v) all reported serious unexpected adverse reactions related to the drug shall be intimated to the Central Licencing Authority and regulatory action resulting from their review shall be complied with;

(vi) no claims except those mentioned above shall be made for the drug without prior approval of the Central Licencing Authority;

(vii) specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Central Licencing Authority before the drugs is marketed;

(viii) if long-term stability data submitted do not cover the proposed shelf-life of the product, the stability study shall be continued to firmly establish the shelf-life and the complete stability data shall be submitted.

83. Licence to manufacture a new drug for sale or for distribution under Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission granted under rule 81, the person intending to manufacture a new drug for sale shall make an application for grant of licence to manufacture for sale or for distribution in accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission in Form CT-22 or Form CT-23, as the case may be, obtained by the applicant from the Central Licencing Authority to manufacture the new drug.

84. Suspension or cancellation of permission.— (1) Where the manufacturer fails to comply with any provisions of the Act, these rules and any condition of the permission, the Central Licencing Authority may, after affording an opportunity of being heard, suspend or cancel the permission for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates.

(2) Where the manufacturer whose permission has been suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, such manufacturer may, within thirty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as considered appropriate.

85. Responsibility of importers or manufacturers in marketing of new drugs.— The manufacturer or importer of new drugs shall be responsible for marketing a new drug for the approved indication and in only such dosage form for which it has been permitted:

Provided that the manufacturer or importer of new drug shall not be punished for the consequences resulting from use of the drug for an indication other than for which the drug has been approved where the manufacturer proves that he has not been involved in any manner in the promotion of use of the new drug for other than approved indication.

CHAPTER XI

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IMPORT OR MANUFACTURE OF UNAPPROVED NEW DRUG FOR TREATMENT OF PATIENTS IN GOVERNMENT HOSPITAL AND GOVERNMENT MEDICAL INSTITUTION

86. Application for import of unapproved new drug by Government hospital and Government medical institution.— (1) Notwithstanding anything contained in these rules, a medical officer of a Government hospital or a Government medical institution, may import new drug, which has not been permitted in the country under Chapter X of these rules, but approved for marketing in the country of origin for treatment of a patient suffering from life threatening disease or disease causing serious permanent disability or disease requiring therapies for unmet medical needs, by making an application duly certified by the Medical Superintendent of the Government hospital or Head of the Government medical institution, as the case may be, to the Central Licencing Authority in Form CT-24.

(2) The application under sub-rule (1) shall be accompanied by such other particulars and documents as are specified in Form CT-24 along with fee as specified in the Sixth Schedule.

87. Grant of licence for import of unapproved new drug by Government hospital and medical institution.— (1)The Central Licencing Authority, after scrutiny of information and documents enclosed with the application and such further enquiry, if any, as considered necessary, may,—

(i) if satisfied, that the requirements of these rules have been complied with, grant licence for import of an unapproved new drug by Government hospital and Government medical institution in Form CT-25;

(ii) if not satisfied with the requirements as referred to in sub-clause (i), reject the application, for reasons to be recorded in writing, within a period of ninety days, from the date of application made under sub-rule (1) of rule 86.

(2) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1), may file an appeal before the Central Government within forty-five days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days from the date of filing the appeal.

(3) The quantity of any single drug imported on the basis of licence granted under sub-rule (1), shall not exceed one hundred average dosages per patient but in exceptional circumstances and on being satisfied about the necessity and exigency the Central Licencing Authority may allow import of unapproved new drugs in larger quantities depending on the condition and requirement of such patient.

88. Conditions of licence.— The import licence granted under rule 87 in Form CT-25 shall be subject to the following conditions, namely:—

(i) the licence shall remain valid for a period of three years from the date it has been issued;

(ii) the licence shall be displayed in the premises of the medical institution including where the unapproved new drug is being stocked and used in the office of the Medical Superintendent of the Government hospital or Head of Government medical institution;

(iii) the licencee shall stock the unapproved new drug imported under this licence under proper storage conditions;

(iv) the unapproved new drug imported under this licence shall be exclusively used for treatment of the patient and supplied under the supervision of a registered pharmacist and no part of such unapproved new drug shall be sold in the market or supplied to any other person, agency, institution or place;

(v) the registered pharmacist shall maintain a record as specified in Annexure of Form CT-25, countersigned by the Medical Superintendent of the Government hospital or Head of the Government medical institution which shall be produced, on demand by the officer authorised by the Central Licencing Authority under these rules;

(vi) the Government hospital and Government medical institution referred to in sub-rule (1) of rule 87, shall submit to the Central Licencing Authority a half yearly report about the status and stock of unapproved new drugs imported, utilised and destroyed;

(vii) where the unapproved new drugs imported under licence granted under sub-rule (1) of rule 87, are left over or remain unused or get damaged or its specified shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed and the action taken in respect thereof be recorded as referred to in clause(iv) by the registered pharmacist.

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89. Suspension or cancellation of import licence for unapproved new drug of Government hospital or Government medical institution.— (1) Where any licencee referred to rule 87, fails to comply with any provision of the Act and these rules, the Central Licencing Authority, may after affording an opportunity of being heard, by an order in writing, suspend or cancel the permission for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates.

(2) Where the licencee, whose licence has been suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, he may, within a period of forty-five days from the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as considered appropriate.

90. Inspection of unapproved new drug imported by Government hospital or Government medical institution.— The licencee referred in rule 87, shall allow any person authorised by the Central Licencing Authority who may be accompanied by an officer authorised by the State Licencing Authority, to enter the premises where the unapproved new drugs are stored and is being used, with or without prior notice, and records, to inspect such premises, store and record, investigate the manner in which the drugs are being used and stocked and to take sample thereof.

91. Application for permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease.— (1) Where any medical officer of a Government hospital or Government medical institution prescribes in special circumstances any new drug for a patient suffering from serious or life threatening disease for which there is no satisfactory therapy available in the country and which is not yet approved by the Central Licencing Authority but the same is under clinical trial in the country, then, such new drug may be approved to be manufactured in limited quantity subject to provisions of these rules.

(2) Where any manufacturer intends to manufacture new drug referred to in sub-rule (1), he shall obtain the consent in writing from the patient to whom the unapproved new drug has been prescribed under sub-rule (1) or his legal heirs and make an application to the Ethics Committee of the Government hospital or medical institution, as the case may be for obtaining its specific recommendation for manufacture of such unapproved new drug.

(3) After obtaining the recommendation of the Ethics Committee under sub-rule (2), the manufacturer shall make an application in Form CT-26 to obtain the permission to the Central Licencing Authority for manufacturing specific new drug.

(4) The application under sub-rule (3) shall be accompanied by consent in writing from the patient referred to in sub-rule (1) or his legal heirs regarding use of such unapproved new drug and such other particulars and documents as are specified in Form CT-26 along with fee as specified in the Sixth Schedule.

92. Grant of permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease.— (1) The Central Licencing Authority may, after scrutiny of information and documents enclosed with the application and such further enquiry, if any, as considered necessary,-

(i) if satisfied, that the requirements of these rules have been complied with, grant permission to manufacture unapproved new drug but under clinical trial for treatment of patient of serious or life threatening disease in Form CT-27;

(ii) if not satisfied with the requirements as referred to in clause (i), reject the application, for reasons to be recorded in writing, within a period of ninety days, from the date of application made under rule 91.

(2) The quantity of any single new drug manufactured on the basis of permission granted under sub-rule (1) shall not exceed one hundred average dosages per patient but in exceptional circumstances on the basis of the prescription of the medical officer referred to in sub-rule (1) and the recommendation of the Ethics Committee, the Central Licencing Authority may allow the manufacture of such new drug in larger quantity.

93. Condition of permission.— The permission granted under rule 92 in Form CT-27, is subject to the following conditions, namely:-

(i) the permission shall remain valid for a period of one year from the date it has been issued;

(ii) the patient to whom the unapproved new drug is prescribed under sub-rule (1) of rule 92 shall use such unapproved new drug under the supervision of the medical officer at the place specified in the permission or at such other places, as the Central Licencing Authority may authorise;

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(iii) the manufacturer to whom the permission is granted under sub-rule (1) of rule 92, shall make use of the unapproved new drug only for the purposes specified in the permission and no part of it shall be sold in the market or supplied to any other person, agency, institution or place;

(iv) the manufacturer referred to in clause (iii) shall keep record of the unapproved new drugs manufactured, stored and supplied by him to the patient in a register in the format as specified in annexure of Form CT-27;

(v) the manufacturer referred to in clause (iii), shall submit to the Central Licencing Authority a half yearly report about the status of the unapproved new drugs manufactured, supplied to the authorised patient;

(vi) the manufactured unapproved new drugs shall be kept and stored in accordance with the storage conditions specified on its label and supplied to the patient under the supervision of the medical officer referred to in sub-rule (1) of rule 91 or a registered pharmacist duly authorised by him;

(vii) the registered pharmacist shall maintain a record of the full name and address of the patients, diagnosis, dosage schedule, total quantity of drugs received and issued, countersigned by the Medical Superintendent of the Government hospital or Head of the medical institution which shall be produced, on demand by the officer authorised by the Central Licencing Authority under the Act;

(viii) where the unapproved new drug manufactured in accordance with the permission issued under sub-rule (1) of rule 92, is left over or remain unused or get damaged or its specified shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed by the manufacturer and the action taken in respect thereof shall be recorded;

(ix) the permission holder shall inform the Central Licencing Authority of the occurrence of any serious adverse event and action taken thereon including any recall within fifteen days of occurrence of such event.

94. Inspection of unapproved new drug but under clinical trial manufactured for patient of life threatening disease.— The manufacturer referred to in rule 92, shall allow persons authorised by the Central Licencing Authority including the person authorised by the State Licencing Authority to enter the premises where the unapproved new drug is being manufactured, stored and supplied, with or without prior notice, to inspect such premises and records, investigate the manner in which the unapproved new drug is being manufactured, supplied and to take sample thereof.

95. Suspension or cancellation of permission to manufacture unapproved new drug but under clinical trial.— (1) Where the manufacturer to whom permission is granted under rule 92 fails to comply with any provision of the Act and these rules, the Central Licencing Authority, may, after giving an opportunity of being heard, by an order, in writing, suspend or cancel the permission for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates.

(2) Where the manufacturer whose permission is suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, he may, within a period of forty-five days from the receipt of the order, make an appeal to the Central Government in respect of suspension or cancellation of the permission and that Government, may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as considered appropriate.

96. Licence to manufacture an unapproved new drug but under clinical trial, for treatment of patient of life threatening disease under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under rule 92, the person intending to manufacture an unapproved new drug, which is under clinical trial, for treatment of patient of serious or life threatening disease, shall make an application for grant of licence to manufacture the unapproved new drug under the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission in Form CT-27 obtained by the applicant from the Central Licencing Authority to import the new drugs.

CHAPTER XII

AMENDEMENTS OF DRUGS AND COSMETICS RULES, 1945

97. **In the Drugs and Cosmetics Rules 1945, after rule 122DA the following new rule shall be inserted, namely:—**

"122DAA. Non-application of certain rules for new drugs and investigational new drugs for human use.— Part XA and Schedule Y shall not be applicable in respect of new drugs and investigational new drugs for human use from the date of coming into force of the New Drugs and Clinical Trials Rules, 2019, and the references in respect of human use made in the these rules shall respectively be omitted, and the construction thereof shall be construed accordingly and shall stand amended with all cogent meaning of the grammar".

CHAPTER XIII

MISCELLANEOUS

98. **Pre-submission meeting.—** (1) Any person who intends to make an application for grant of licence or permission for import or manufacture of new drugs or to conduct clinical trial may, request by making an application in writing, for a pre-submission meeting with the Central Licencing Authority or any other officer authorised by the Central Licencing Authority for seeking guidance about the requirements of law and procedure of such licence or permission of manufacturing process, clinical trial and other requirements.

(2) The application for pre-submission meeting under sub-rule (1) may be accompanied by particulars and documents referred to in the Second Schedule, as available with the applicant to support his proposal along with fee as specified in the Sixth Schedule.

(3) Where the applicant intends to seek guidance about the sale process of new drugs or import licence, in addition to the purposes referred to in sub-rule (2), the fee as specified in the Sixth Schedule shall be submitted along with the application.

(4) Where the Central Licencing Authority is satisfied that the application is incomplete or the information or the documents submitted along with the same are inadequate, he may within a period of thirty days from the receipt of the same intimate the facts to the applicant in writing and direct him to furnish such further information or documents as are necessary in accordance with the provisions of the Act and these rules.

(5) In the pre-submission meeting, the Central Licencing Authority or any other person authorised by it shall provide suitable clarification to the applicant.

99. **Post-submission meeting.—** (1) If the applicant desires to seek clarification in person in respect of pending application and queries related thereto, the applicant may make an application for a post-submission meeting with the officer designated by the Central Licencing Authority within a period of fifteen days from the date the query was received for seeking guidance with regards to the queries concerning pending application.

(2) The applicant shall clearly state the points on which clarification is required and after receipt of such application, the designated officer shall inform the time and date scheduled for post submission meeting.

(3) The summary of the clarification provided by the designated officer shall be made available to the applicant.

(4) The application for post-submission meeting under sub-rule (1) shall be accompanied with the fee as specified in the Sixth Schedule.

(5) In the post submission meeting, the officer designated by the Central Licencing Authority shall provide suitable clarification to the applicant.

100. **Constitution of expert committee or group of experts by Central Licencing Authority.—** The Central Licencing Authority may, when so required, constitute one or more expert committee or group of experts with specialisation in relevant fields, with the approval of Central Government, to evaluate scientific and technical matters relating to drugs and such committee or group may, give its recommendations to that authority on matters referred to it within a period of sixty days from the date of reference.

101. **Name of countries for purpose of new drug approval.—** The Central Licencing Authority, with the approval of the Central Government, may specify, by an order, the name of the countries, from time to time, for considering

waiver of local clinical trial for approval of new drugs under Chapter X and for grant of permission for conduct of clinical trial under Chapter V.

102. Mode of payment of fee.— The fees prescribed under these rules, in case of application made to the Central Licencing Authority, shall be paid through challan or by electronic mode, in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110001 or any other branch of Bank of Baroda, or any other bank, notified by the Ministry of Health and Family Welfare in the Central Government, to be credited under the Head of Account "0210- Medical and Public Health, 04-Public Health, 104-Fees and Fines.

103. Debarment of applicant.— (1) Whoever himself or, any other person on his behalf, or applicant is found to be guilty of submitting misleading, or fake, or fabricated documents, may, after giving him an opportunity to show cause as to why such an order should not be made, in writing, stating the reasons thereof, be debarred by the Central Licencing Authority for such period as deemed fit.

(2) Where an applicant is aggrieved by an order made by the Central Licencing Authority under sub-rule (1), such applicant may, within thirty days from the receipt of the order, make an appeal to that Government and that Government, may, after such enquiry as it considers necessary, and after affording an opportunity of being heard, pass such orders as considered appropriate.

104. Order of suspension or revocation in public domain.— In case, the Central Licencing Authority issue any order of suspension or revocation or cancellation of any permission or licence or registration granted under these rules, such order shall be made available in the public domain immediately by uploading it in the website of Central Drugs Standard Control Organisation.

105. Digitalisation of Forms.— The forms prescribed under these rules may be suitably modified for conversion into digital forms by the Central Drugs Standard Control Organisation and such modification shall not require any amendment in these rules.

106. Applicability in case of inconsistency.— If there is any inconsistency between these rules and any other rule made under the Act, the provisions of these rules shall prevail over such other rules.

107. Savings.— (1) Notwithstanding the non-applicability of the Drugs and Cosmetics Rules, 1945, the approvals or permissions or licences or certificates issued under the provisions of the Act and the said rules in respect of new drugs and investigational new drugs for human use, prior to commencement of these rules, shall be deemed to be valid till its expiry under the corresponding provisions of said rules;

(2) Any things done or any action taken or purported to have been done or taken, including any rule, notification, inspection, order or notice made or issued or any appointment or declaration made or any operation undertaken or any direction given or any proceedings taken or any penalty, punishment, forfeiture or fine imposed under the Drugs and Cosmetics Rules, 1945 shall, be deemed to have been done or taken under the corresponding provisions of these rules and shall always remain valid for all purposes.

FIRST SCHEDULE

(*See rules 19 and 31*)

GENERAL PRINCIPLES AND PRACTICES FOR CLINICAL TRIAL

1. General Principles.— (1) The principles and guidelines for protection of trial subjects as described in Third Schedule as well as Good Clinical Practices guidelines shall be followed in conduct of any clinical trial.

(2) The sponsor and investigator share the responsibilities for the protection of trial subject together with ethics committee. The responsibilities of sponsor, investigator and ethics committee are described in the Third Schedule.

(3) The results of non-clinical studies or previous clinical trials should be sufficient to ensure that the new drugs or investigational new drug is safe for the proposed clinical trial.

(4) Throughout the clinical trial and drug development process, the animal toxicological data and clinical data generated should be evaluated to ensure their impact for the safety of the trial subject.

2. Approach in design and analysis.— (1) Clinical trial should be planned, designed, conducted, analysed and reported according to sound scientific and ethical principles. Following important principles should be followed:

(a) The primary objective of any clinical trial should be clearly and explicitly stated which may include exploratory or confirmatory characterisation of safety, efficacy, assessment of pharmacokinetic and pharmacodynamic parameters;

(b) The clinical trial should be designed appropriately so that it provides the desired information;

(c) Appropriate comparator may be utilised to achieve the objective with respect to primary and secondary end points. Comparison may be made with placebo, no treatment, active controls or of different doses of the new drug or investigational new drug;

(d) The number of subjects to be included in the clinical trial should be adequate depending on the nature and objective of the clinical trial.

3. Development Methodology: (1) Non clinical studies,-

(a) The nature of non-clinical studies and their timing in respect of conduct of clinical trial should be determined taking following aspects in to consideration:

(i) characteristics of the new drug or investigational new drug;

(ii) disease of conditions for which the new drug or investigational new drug is intended to be indicated;

(iii) duration and exposure in clinical trial subject;

(iv) route of administration.

(b) The detailed requirements of non-clinical studies have been specified in the Second Schedule.

(c) For first in human studies the dose should be calculated carefully based on the non-clinical pharmacological, toxicological data generated.

(2) Phases in Clinical Trial: Clinical drug development generally consists of four phases (Phase I-IV). The details of these phases are described as under.

(a) Phase I.— The objective of studies in this phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into humans. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I trial should preferably be carried out by investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the subjects. Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives: -

(a) Maximum tolerated dose: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.

(b) Pharmacokinetics, i.e., characterisation of a drug's absorption, distribution, metabolism and excretion: Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic or pharmacodynamic studies) may be conducted in healthy volunteer subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

(d) Early measurement of drug activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

(b) Phase II.— (i) The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common

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short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this phase is to determine the dose and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

(c) Phase III.— (i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drugs.

(ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies may need to be carried out if scientifically and ethically justified, primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Central Licencing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

In case of an application of a new drug already approved and marketed in other country, where local clinical trial in India is waived off or not found scientifically justified for its approval for manufacturing first time in the country, the bioequivalence studies of such drug, as appropriate, is required to be carried out and the test batches manufactured for the purpose shall be inspected before its approval.

(d) Phase IV.— Phase IV or post marketing trial of new drugs are performed after the approval of the drug and related to the approved indication. Such trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. Such trial might not have been considered essential at the time of new drug approval due to various reasons such as limitation in terms of patient exposure, duration of treatment during clinical development of the drug, need for early introduction of the new drug in the interest of patients etc. Phase IV trials include additional drug-drug interaction, dose response or safety studies and trials design to support use under the approved indication e.g. mortality or morbidity studies, epidemiological studies, etc.

(3) Studies in special populations**.—** Information supporting the use of the drug in children, pregnant women, nursing women, elderly patients, patients with renal or other organ systems failure, and those on specific concomitant medication is required to be submitted if relevant to the clinical profile of the drug and its anticipated usage pattern.

(A) ***Geriatrics*****.—** Geriatric patients should be included in Phase III clinical trials (and in Phase II trials, at the Sponsor's option) in meaningful numbers, if—

(a) the disease intended to be treated is characteristically a disease of aging; or

(b) the population to be treated is known to include substantial numbers of geriatric patients; or

(c) when there is specific reason to expect that conditions common in the elderly are likely to be encountered; or

(d) when the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

(B) ***Paediatrics*****.—** (i) The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate

age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

(ii) If the new drug is for diseases predominantly or exclusively affecting paediatric patients, clinical trial data should be generated in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

(iii) If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

(iv) If the new drug has a potential for use in paediatric patients – paediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited paediatric data at the time of submission of application, more data in paediatric patients would be expected after marketing authorisation for use in children is granted.

(v) The paediatric studies should include—

(a) clinical trials,

(b) relative bioequivalence comparisons of the paediatric formulation with the adult formulation performed in adults, and definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the drug is likely to be used. These studies should be conducted in the paediatric patient population with the disease under study.

(vi)If the new drug is a major therapeutic advance for the paediatric population the studies should begin early in the drug development, and this data should be submitted with the new drug application.

(vii) For clinical trials conducted in the paediatric population, the reviewing ethics committee should include members who are knowledgeable about paediatric, ethical, clinical and psychosocial issues.

(C) Pregnant or nursing women.— (i) Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant or nursing women or fetuses or nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.

(ii) For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, foetus and child will be required. Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug.

4. Conduct of Clinical Trial.— Clinical trial should be conducted in accordance with the principles as specified in Third Schedule. Adherence to the clinical trial protocol is essential and if amendment of the protocol becomes necessary the rationale for the amendment shall be provided in the form of a protocol amendment. Serious adverse events shall be reported during clinical trial in accordance with these Rules.

5. Analysis.— The results of a clinical trial shall be analysed according to the plan specified in the clinical trial protocol. Safety data should be appropriately tabulated and all adverse events should be classified according to their seriousness and causal relationship with the study drug.

6. Reporting.— Report of clinical trial shall be documented in accordance with the approaches specified in Table 6 of the Third Schedule. The report shall be certified by the principal investigator or if no principal investigator is designated then by each of the participating investigators of the study.

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SECOND SCHEDULE

(*See rules 21, 75, 80 and 97*)

REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT OR MANUFACTURE OF NEW DRUG FOR SALE OR TO UNDERTAKE CLINICAL TRIAL

1. Application for permission.— (1) Application for permission to import or manufacture new drug for sale or to undertake clinical trials under these Rules shall be made to the Central Licencing Authority accompanied with following data in accordance with the Table 1 or Table 2 or Table 3 or Table 4 of this Schedule, as the case may be, namely:-

(i) chemical and pharmaceutical information;

(ii) animal pharmacology data;

(a) specific pharmacological actions and demonstrating, therapeutic potential for humans shall be described according to the animal models and species used. Wherever possible, dose-response relationships and ED_{50} shall be submitted. Special studies conducted to elucidate mode of action shall also be described;

(b) general pharmacological actions;

(c) pharmacokinetic data related to the absorption, distribution, metabolism and excretion of the test substance. Wherever possible, the drug effects shall be co-related to the plasma drug concentrations;

(iii) animal toxicology data;

(iv) human clinical pharmacology data as prescribed and as stated below:-

(a) for new drug substances discovered or developed in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as prescribed;

(b) for new drug substances discovered or developed in countries other than India, Phase I data should be submitted along with the application. After submission of Phase I data generated outside India to the Central Licensing Authority, permission may be granted to repeat Phase I trials or to conduct Phase II trials and subsequently Phase III trial concurrently with other global trials for that drug. For a drug going to be introduced for the first time in the country, Phase III trial may be required to be conducted in India before permission to market the drug is granted unless otherwise exempted;

(c) the data required will depend upon the purpose of the new drug application. The number of study subjects and sites to be involved in the conduct of clinical trial will depend upon the nature and objective of the study. Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier phases;

(d) application for permission to initiate specific phase of clinical trial should also accompany investigator's brochure as per Table 7 of Third Schedule, proposed protocol as per Table 2 of Third Schedule, case record form, trial subject's informed consent document as per Table 3 of Third Schedule, investigator's undertaking as per Table 4 of Third Schedule and ethics committee clearance, if available as per Table 1 of Third Schedule;

(e) reports of clinical studies submitted should be in consonance with the format specified in Table 6 of Third Schedule. The study report shall be certified by the principal investigator or, if no principal investigator is designated, then by each of the investigators participating in the study. The certification should acknowledge the contents of the report, the accurate presentation of the study was undertaken, and express agreement with the conclusions. Each page should be numbered;

(v) regulatory status in other countries as prescribed including information in respect of restrictions imposed, if any, on the use of the drug in other countries, e.g. dosage limits, exclusion of certain age groups, warning about adverse drug reactions etc. Likewise, if the drug has been withdrawn in any country by the manufacturer or by regulatory authorities, such information should also be furnished along with the reasons and their relevance, if any, to India. This information must continue to be submitted by the sponsor to the Central Licencing Authority during the course of marketing of the drug in India;

(vi) the full prescribing information should be submitted as part of the new drug application for marketing. The format of prescribing information is specified in Table 8 of Third Schedule.

(vii) all package inserts, promotional literature and patient education material subsequently produced are required to be consistent with the contents of the approved full prescribing information. The drafts of label and carton texts should comply with provisions of rule 96 and rule 97 of the Drugs and Cosmetics Rules, 1945. After submission and approval by the Central Licencing Authority, no changes in the package insert shall be effected without such changes being approved by the Central Licencing Authority;

(viii) complete testing protocol for quality control testing together with a complete impurity profile and release specifications for the product as prescribed should be submitted as part of new drug application for marketing. Samples of the pure drug substance and finished product are to be submitted when desired by the regulatory authority;

(ix) if the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Central Licencing Authority along with the application.

(2) Special situations for a new drug where relaxation, abbreviations, omission or deferment of data may be considered. - (i) Depending on categories and nature of new drugs to be imported or manufactured for sale or clinical trial to be undertaken (viz. New Chemical Entity, biological products, similar biologics, approved new drug or new dosage form or new indication or new route of administration or new strength of already approved drugs, etc.,) requirements of chemical and pharmaceutical information, animal pharmacology and toxicology data, clinical data may differ. The requirements may also differ depending on the specific phase of clinical trial proposed to be conducted as well as clinical parameters related to the specific study drug.

(ii) For drugs intended to be used in life threatening or serious disease conditions or rare diseases and for drugs intended to be used in the diseases of special relevance to Indian scenario or unmet medical need in India, disaster or special defence use e.g. haemostatic and quick wound healing, enhancing oxygen carrying capacity, radiation safety, drugs for combating chemical, nuclear, biological infliction etc., following mechanism may be followed to expedite the development of new drug and approval process.

(A) Accelerated Approval Process: Accelerated approval process may be allowed to a new drug for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of alternative treatments, provided that there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment.

(a) In such case, the approval of the new drug may be based on data generated in clinical trial where surrogate endpoint shall be considered rather than using standard outcome measures such as survival or disease progression, which are reasonably likely to predict clinical benefit, or a clinical endpoint. These should be measurable earlier than irreversible morbidity or mortality (IMM) and reasonably likely to predict clinical benefit.

(b) After granting accelerated approval for such drug, the post marketing trials shall be required to validate the anticipated clinical benefit.

(c) Accelerated approval may also be granted to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease of special relevance to the country, and addresses unmet medical needs. This provision is intended to facilitate and expedite review of drugs so that an approved product can reach the therapeutic armamentarium expeditiously.

(d) If the remarkable efficacy is observed with a defined dose in the Phase II clinical trial of investigational new drug for the unmet medical needs of serious and life threatening diseases in the country, it may be considered for grant of marketing approval by the Central Licencing Authority based on Phase II clinical trial data. In such cases, additional post licensure studies may be required to be conducted after approval to generate the data on larger population to further verify and describe the clinical benefits, as per the protocol approved by the Central Licencing Authority.

(e) The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development. Early in development, such potential should be sufficiently demonstrated based on nonclinical models, a mechanistic rationale and pharmacologic data. Later in development, prior to new drug approval such potential should be demonstrated through clinical data to address an unmet medical need.

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Explanation. - For the purpose of this clause, an unmet medical need is a situation where treatment or diagnosis of disease or condition is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).

(B) Situations where quick or expeditious review process can be sought for approval of a new drug after clinical development: - (i) In situation where the evidence for clinical safety and efficacy have been established even if the drug has not completed the all or normal clinical trial phases, the sponsor or applicant may apply to the licencing authority for expedited review process wherein the licencing authority will examine and satisfy the following conditions. -

(a) it is for a drug that is intended to treat a serious or life threatening or rare disease or condition;

(b) if approved, the drug would provide a significant advantage in terms of safety or efficacy;

(c) there is substantial reduction of a treatment-limiting adverse reaction and enhancement of patient compliance that is expected to lead to an improvement in serious outcomes;

(ii) the sponsor or applicant may also apply to the licencing authority for expedited review process for new drugs developed for disaster or defence use in extraordinary situation, such as war time, the radiation exposure by accident or intention, sudden deployment of forces at areas with higher health risk, where specific preventive and treatment strategy is required, where new intervention in the form of new drug, route of delivery or formulation has been developed and where real life clinical trial may not be possible. The permission for manufacture of such new drug may be granted if following conditions are satisfied: -

(a) The preclinical data makes a case for claimed efficacy;

(b) there is no possibility of obtaining informed consent from the patient or his legally acceptable representative, as the case may be, adopting inclusion and exclusion criteria and strict protocol adherence by each subject;

(c) there is no established management or therapeutic strategy available as on date and proposed intervention has clear possible advantage;

(d) such approval can be used only for one time. The subsequent approval shall only be granted once detailed efficacy report of such intervention is generated.

(iii) the new drug is an orphan drug as defined in clause (x) of rule 2 of these Rules.

(3) Requirements of data and information for permission to import or manufacture of a drug already approved which is now proposed to be clinically tried or marketed with certain new claims. – (i) In case a drug already approved by the Central Licencing Authority for certain claims, which is now proposed to be clinically tried or marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration or novel drug delivery system (NDDS), the requirements of data and information for permission to import or manufacture of such new drug for sale or to undertake clinical trial shall depend on nature and regulatory status of the drug for the new claim in other country. Application for approval of manufacture or import of such new drug or to undertake Clinical trial may differ from application for a new drug molecule in that they allow the applicant and regulatory authority to rely at least in part, on the safety or efficacy data of drug formulation already approved. However, additional non-clinical or clinical data may be necessary to substantiate the new claims considering the following:-

(A) Chemical and pharmaceutical information will be same as prescribed in this Schedule. However, the data requirements may be omitted depending on whether the drug formulation is already approved and marketed in the country by the applicant in the same dosage form for certain indication. If it is approved and marketed, no further chemical and pharmaceutical data is required to be submitted.

(B) The animal pharmacological and toxicological data and clinical data needed in such cases will usually be determined on case-by-case basis depending on the type of new claims being made by the applicant as well as the mechanism of action, patho-physiology of the disease or condition, safety and efficacy profile in the respective conditions or population and clinical data already generated with the drug in the approved claim. The

requirements may be abbreviated or relaxed or omitted as considered appropriate by the Central Licencing Authority under following conditions:

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(a) the drug is already approved and marketed in other country for the proposed new claim;

(b) clinical data supporting the benefit-risk ratio in favour of the drug in the proposed new claim is available;

(c) the clinical trial doesn't involve a route of administration, dose, patient population that significantly increases the risk associated with the use of the drug.

(ii) In case of an application for permission to undertake clinical trial of a new drug formulation, which is already approved in the country, no chemical and pharmaceutical data and non-clinical and clinical data is required to be submitted provided the clinical trial is proposed to be conducted with a new drug manufactured or imported by a firm under necessary new drug permission or import registration and licence, as the case may be granted by the Central Licencing Authority.

Note: The data requirements stated in this Schedule are expected to provide adequate information to evaluate the efficacy, safety and therapeutic rationale of new drugs prior to the permission for sale. Depending upon the nature of new drugs and diseases, additional information may be required by the Central Licencing Authority. The applicant shall certify the authenticity of the data and documents submitted in support of an application for new drug. The Central Licencing Authority reserves the right to reject any data or any documents if such data or contents of such documents are found to be of doubtful integrity.

2. Animal toxicology (Non-clinical toxicity studies).- (1) General principles. - Toxicity studies should comply with the norms of Good Laboratory Practices (GLP). Briefly, these studies should be performed by suitably trained and qualified staff employing properly calibrated and standardized equipment of adequate size and capacity. Studies should be done as per written protocols with modifications (if any) verifiable retrospectively. Standard operating procedures (SOPs) should be followed for all managerial and laboratory tasks related to these studies. Test substances and test systems (in-vitro or in-vivo) should be properly characterised and standardized. All documents belonging to each study, including its approved protocol, raw data, draft report, final report, and histology slides and paraffin tissue blocks should be preserved for a minimum of five years after marketing of the drug.

Toxicokinetic studies (generation of pharmacokinetic data either as an integral component of the conduct of non-clinical toxicity studies or in specially designed studies) should be conducted to assess the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study. Other objectives of toxicokinetic studies include obtaining data to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety, to support the choice of species and treatment regimen in nonclinical toxicity studies and to provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies.

(1.1) Systemic toxicity studies,-

(1.1.1) Single-dose toxicity studies**.—** These studies (see Table 1) should be carried out in 2 rodent species (mice and rats) using the same route as intended for humans. In addition, unless the intended route of administration in humans is only intravenous, at least one more route should be used in one of the species to ensure systemic absorption of the drug. This route should depend on the nature of the drug. A limit of 2g/kg (or 10 times the normal dose that is intended in humans, whichever is higher) is recommended for oral dosing. Animals should be observed for 14 days after the drug administration, and Minimum Lethal Dose (MLD) and Maximum Tolerated Dose (MTD) should be established. If possible, the target organ of toxicity should also be determined. Mortality should be observed for up to seven days after parenteral administration and up to 14 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD_{10} and LD_{50} should be reported preferably with 95 percent confidence limits. If LD_{50} cannot be determined, reasons for the same should be stated.

The dose causing severe toxic manifestations or death should be defined in the case of cytotoxic anticancer agents, and the post-dosing observation period should be up to 14 days. Mice should first be used for determination of MTD. Findings should then be confirmed in rat for establishing linear relationship between toxicity and body surface area. In case of nonlinearity, data of the more sensitive species should be used to determine the Phase I starting dose. Where rodents are known to be poor

predictors of human toxicity (e.g., antifolates), or where the cytotoxic drug acts by a novel mechanism of action, Maximum Tolerated Dose (MTD) should be established in non-rodent species. 101

(1.1.2) Repeated-dose systemic toxicity studies.— These studies (see Table 1) should be carried out in at least two mammalian species, of which one should be a non-rodent. Dose ranging studies should precede the 14-, 28-, 90- or 180- day toxicity studies. Duration of the final systematic toxicity study will depend on the duration, therapeutic indication and scale of the proposed clinical trial. If a species is known to metabolise the drug in the same way as humans, it should be preferred for toxicity studies.

In repeated-dose toxicity studies the drug should be administered seven days a week by the route intended for clinical use. The number of animals required for these studies, i.e. the minimum number of animals on which data should be available.

Wherever applicable, a control group of animals given the vehicle alone should be included, and three other groups should be given graded doses of the drug. The highest dose should produce observable toxicity; the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it. To make allowance for the sensitivity of the species the intermediate dose should cause some symptoms, but not gross toxicity or death, and should be placed logarithmically between the other two doses.

The parameters to be monitored and recorded in long-term toxicity studies should include behavioural, physiological, biochemical and microscopic observations. In case of parenteral drug administration, the sites of injection should be subjected to gross and microscopic examination. Initial and final electrocardiogram and fundus examination should be carried out in the non-rodent species.

In the case of cytotoxic anticancer agents dosing and study design should be in accordance with the proposed clinical schedule in terms of days of exposure and number of cycles. Two rodent species may be tested for initiating Phase I trials. A non-rodent species should be added if the drug has a novel mechanism of action, or if permission for Phase II, III or marketing is being sought.

For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half-life, incomplete elimination or unanticipated organ toxicity.

Notes: (i) Single dose toxicity study. - Each group should contain at least five animals of either sex. At least four graded doses should be given. Animals should be exposed to the test substance in a single bolus or by continuous infusion or several doses within 24 hours. Animals should be observed for 14 days. Signs of intoxication, effect on body weight, gross pathological changes should be reported. It is desirable to include histo-pathology of grossly affected organs, if any.

(ii) Dose-ranging study. - Objectives of this study include the identification of target organ of toxicity and establishment of Maximum Tolerated Dose (MTD) for subsequent studies.

(a) Rodents. - Study should be performed in one rodent species (preferably rat) by the proposed clinical route of administration. At least four graded doses including control should be given, and each dose group as well as the vehicle control should consist of a minimum of five animals of each sex. Animals should be exposed to the test substance daily for 10 consecutive days. Highest dose should be the maximum tolerated dose of single-dose study. Animals should be observed daily for signs of intoxication (general appearance, activity and behavior etc), and periodically for the body weight and laboratory parameters. Gross examination of viscera and microscopic examination of affected organs should be done.

(b) Non-rodents. - One male and one female are to be taken for ascending Phase Maximum Tolerated Dose (MTD) study. Dosing should start after initial recording of cage-side and laboratory parameters. Starting dose may be three to five times the extrapolated effective dose or Maximum Tolerated Dose (MTD) (whichever is less), and dose escalation in suitable steps should be done every third day after drawing the samples for laboratory parameters. Dose should

be lowered appropriately when clinical or laboratory evidence of toxicity are observed. Administration of test substance should then continue for 10 days at the well-tolerated dose level following which, samples for laboratory parameters should be taken. Sacrifice, autopsy and microscopic examination of affected tissues should be performed as in the case of rodents.

(iii) 14-28 Day repeated-dose toxicity studies. - One rodent (6-10/sex/group) and one non-rodent (2-3/sex/group) species are needed. Daily dosing by proposed clinical route at three dose levels should be done with highest dose having observable toxicity, mid dose between high and low dose, and low dose. The doses should preferably be multiples of the effective dose and free from toxicity. Observation parameters should include cage side observations, body weight changes, food or water intake, blood biochemistry, haematology, and gross and microscopic studies of all viscera and tissues.

(iv) 90 Days repeated-dose toxicity studies. - One rodent (15-30/sex/group) and one non-rodent (4-6/sex/group) species are needed. Daily dosing by proposed clinical route at three graded dose levels should be done. In addition to the control a "high-dose-reversal" group and its control group should be also included. Parameters should include signs of intoxication (general appearance, activity and behavior etc), body weight, food intake, blood biochemical parameters, haematological values, urine analysis, organ weights, gross and microscopic study of viscera and tissues. Half the animals in "reversal" groups (treated and control) should be sacrificed after 14 days of stopping the treatment. The remaining animals should be sacrificed after 28 days of stopping the treatment or after the recovery of signs or clinical pathological changes – whichever comes later, and evaluated for the parameters used for the main study.

(v) 180-Day repeated-dose toxicity studies. - One rodent (15-30/sex/group) and one non-rodent (4-6/sex/group) species are needed. At least four groups, including control, should be taken. Daily dosing by proposed clinical route at three graded dose levels should be done. Parameters should include signs of intoxication, body weight, food intake, blood biochemistry, hematology, urine analysis, organ weights, gross and microscopic examination of organs and tissues.

(1.2) Male fertility study: One rodent species (preferably rat) should be used. Dose selection should be done from the results of the previous 14 days or 28 days toxicity study in rat. Three dose groups, the highest one showing minimal toxicity in systemic studies, and a control group should be taken. Each group should consist of six adult male animals. Animals should be treated with the test substance by the intended route of clinical use for minimum 28 days and maximum 70 days before they are paired with female animals of proven fertility in a ratio of 1:2 for mating. Drug treatment of the male animals should continue during pairing. Pairing should be continued till the detection of vaginal plug or 10 days, whichever is earlier. Females getting thus pregnant should be examined for their fertility index after day 13 of gestation. All the male animals should be sacrificed at the end of the study. Weights of each testis and epididymis should be separately recorded. Sperms from one epididymis should be examined for their motility and morphology. The other epididymis and both testes should be examined for their histology.

(1.3) Female reproduction and developmental toxicity studies: These studies need to be carried out for all drugs proposed to be studied or used in women of child bearing age. Segment I, II and III studies (see below) are to be performed in albino mice or rats, and segment II study should include albino rabbits also as a second test species. On the occasion, when the test article is not compatible with the rabbit (e.g. antibiotics which are effective against gram positive, anaerobic organisms and protozoas) the Segment II data in the mouse may be substituted.

(1.3.1) Female fertility study (Segment I). - The study should be done in one rodent species (rat preferred). The drug should be administered to both males and females, beginning a sufficient number of days (28 days in males and 14 days in females) before mating. Drug treatment should continue during mating and, subsequently, during the gestation period. Three graded doses should be used, the highest dose (usually the Maximum Tolerated Dose (MTD) obtained from previous systemic toxicity studies) should not affect general health of the parent animals. At least 15 males and 15 females should be used per dose group. Control and the treated groups should be of similar size. The route of administration should be the same as intended for therapeutic use.

Dams should be allowed to litter and their medication should be continued till the weaning of pups. Observations on body weight, food intake, clinical signs of intoxication, mating behaviour, progress of

gestation or parturition periods, length of gestation, parturition, postpartum health and gross pathology (and histopathology of affected organs) of dams should be recorded. The pups from both treated and control groups should be observed for general signs of intoxication, sex-wise distribution in different treatment groups, body weight, growth parameters, survival, gross examination, and autopsy. Histopathology of affected organs should be done.

(1.3.2) Teratogenicity study (Segment II). - One rodent (preferably rat) and one non-rodent (rabbit) species are to be used. The drug should be administered throughout the period of organogenesis, using three dose levels as described for segment I. The highest dose should cause minimum maternal toxicity and the lowest one should be proportional to the proposed dose for clinical use in humans or a multiple of it. The route of administration should be the same as intended for human therapeutic use.

The control and the treated groups should consist of at least 20 pregnant rats (or mice) and 12 rabbits, on each dose level. All foetuses should be subjected to gross examination, one of the foetuses should be examined for skeletal abnormalities and the other half for visceral abnormalities. Observation parameters should include: (Dams) signs of intoxication, effect on body weight, effect on food intake, examination of uterus, ovaries and uterine contents, number of corpora lutea, implantation sites, resorptions (if any); and for the foetuses, the total number, gender, body length, weight and gross or visceral or skeletal abnormalities, if any.

(1.3.3) Perinatal study (Segment III). - This study is specially recommended if the drug is to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development. One rodent species (preferably rat) is needed. Dosing at levels comparable to multiples of human dose should be done by the intended clinical route. At least four groups (including control), each consisting of 15 dams should be used. The drug should be administered throughout the last trimester of pregnancy (from day 15 of gestation) and then the dose that causes low foetal loss should be continued throughout lactation and weaning. Dams should then be sacrificed and examined as described below.

One male and one female from each litter of F1 generation (total 15 males and 15 females in each group) should be selected at weaning and treated with vehicle or test substance (at the dose levels described above) throughout their periods of growth to sexual maturity, pairing, gestation, parturition and lactation. Mating performance and fertility of F1 generation should thus be evaluated to obtain the F2 generation whose growth parameters should be monitored till weaning. The criteria of evaluation should be the same as described earlier.

Animals should be sacrificed at the end of the study and the observation parameters should include (Dams) body weight, food intake, general signs of intoxication, progress of gestation or parturition periods and gross pathology (if any); and for pups, the clinical signs, sex-wise distribution in dose groups, body weight, growth parameters, gross examination, survival and autopsy (if needed) and where necessary, histopathology.

(1.4) Local toxicity.- These studies are required when the new drug is proposed to be used by some special route (other than oral) in humans. The drug should be applied to an appropriate site (e.g., skin or vaginal mucous membrane) to determine local effects in a suitable species. Typical study designs for these studies should include three dose levels and untreated or vehicle control, preferably use of two species, and increasing group size with increase in duration of treatment. Where dosing is restricted due to anatomical or humane reasons, or the drug concentration cannot be increased beyond a certain level due to the problems of solubility, pH or tonicity, a clear statement to this effect should be given. If the drug is absorbed from the site of application, appropriate systemic toxicity studies will also be required.

Notes: (i) ***Dermal toxicity study*****.** - The study may be done in rabbit and rat. The initial toxicity study shall be carried out by non-animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines. In rabbit and rat studies, daily topical (dermal) application of test substance in its clinical dosage form should be done.; Test material should be applied on shaved skin covering not less than 10% of the total body surface area. Porous gauze dressing should be used to hold liquid material in place. Formulations with different concentrations (at least 3) of test substance, several fold higher than the clinical dosage form should be used. Period of application may vary from seven to 90 days depending on the clinical duration of use. Where skin irritation is grossly visible in the initial studies, a recovery group should be included in the subsequent

repeated-dose study. Local signs (erythema, oedema and eschar formation) as well as histological examination of sites of application should be used for evaluation of results.

(ii) ***Photo-allergy or dermal photo-toxicity***. - It should be tested by Armstrong or Harber test in guinea pig. This test should be done if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential (e.g., drugs to be used in treatment of leucoderma). Pretest in eight animals should screen four concentrations (patch application for two hours ±15 min.) with and without UV exposure (10 J/cm2). Observations recorded at 24 and 48 hours should be used to ascertain highest non-irritant dose. Main test should be performed with 10 test animals and five controls. Induction with the dose selected from pretest should use 0.3 ml/patch for 2 hour ±15 min. followed by 10 J/cm2 of UV exposure. This should be repeated on day 0, 2,4,7,9 and 11 of the test. Animals should be challenged with the same concentration of test substance between day 20 to 24 of the test with a similar 2-hour application followed by exposure to 10 J/cm2 of UV light. Examination and grading of erythema and oedema formation at the challenge sites should be done 24 and 48 hours after the challenge. A positive control like musk ambrett or psoralin should be used.

(iii) ***Vaginal toxicity test*. -** Study is to be done in rabbit or dog. Test substance should be applied topically (vaginal mucosa) in the form of pessary, cream or ointment. Six to ten animals per dose group should be taken. Higher concentrations or several daily applications of test substance should be done to achieve multiples of daily human dose. The minimum duration of drug treatment is seven days (more according to clinical use), subject to a maximum of 30 days. Observation parameters should include swelling, closure of in troit us and histopathology of vaginal wall.

(iv) ***Rectal tolerance test*.-** For all preparations meant for rectal administration this test may be performed in rabbits or dogs. Six to ten animals per dose group should be taken. Formulation in volume comparable to human dose (or the maximum possible volume) should be applied once or several times daily, per rectally, to achieve administration of multiples of daily human dose. The minimum duration of application is seven days (more according to clinical use), subject to a maximum of 30 days. Size of suppositories may be smaller, but the drug content should be several fold higher than the proposed human dose. Observation parameters should include clinical signs (sliding on backside), signs of pain, blood or mucus in faeces, condition of anal region or sphincter, gross and (if required) histological examination of rectal mucosa.

(v) ***Parenteral drugs*.-** For products meant for intravenous or intramuscular or subcutaneous or intradermal injection the sites of injection in systemic toxicity studies should be specially examined grossly and microscopically. If needed, reversibility of adverse effects may be determined on a case to case basis.

(vi) ***Ocular toxicity studies (for products meant for ocular instillation). -*** These studies should be carried out in two species, one of which should be the albino rabbit which has a sufficiently large conjunctival sac. Direct delivery of drug onto the cornea in case of animals having small conjunctival sacs should be ensured. Liquids, ointments, gels or soft contact lenses (saturated with drug) should be used. Initial single dose application should be done to decide the exposure concentrations for repeated-dose studies and the need to include a recovery group. Such initial toxicity studies shall be carried out by non-animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines. Duration of the final study will depend on the proposed length of human exposure subject to a maximum of 90 days. At least two different concentrations exceeding the human dose should be used for demonstrating the margin of safety. In acute studies, one eye should be used for drug administration and the other kept as control. A separate control group should be included in repeated-dose studies. Slit-lamp examination should be done to detect the changes in cornea, iris and aqueous humor. Fluorescent dyes (sodium fluorescein, 0.25 to 1.0%) should be used for detecting the defects in surface epithelium of cornea and conjunctiva. Changes in intra-ocular tension should be monitored by a tonometer. Histological examination of eyes should be done at the end of the study after fixation in Davidson's or Zenker's fluid.

(vii) ***Inhalation toxicity studies*. -** The studies are to be undertaken in one rodent and one non-rodent species using the formulation that is to be eventually proposed to be marketed. Acute, subacute and chronic toxicity studies should be performed according to the intended duration of human exposure. Standard systemic toxicity study designs (described above) should be used. Gases and vapours should be given in whole body exposure chambers; aerosols are to be given by nose-only method. Exposure time and concentrations of test substance (limit dose of 5mg/l) should be adjusted to ensure exposure at levels comparable to multiples of intended human exposure. Three dose groups and a control (plus vehicle control, if needed) are required.

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Duration of exposure may vary subject to a maximum of 6 hours per day and five days a week. Food and water should be withdrawn during the period of exposure to test substance.

Temperature, humidity and flow rate of exposure chamber should be recorded and reported. Evidence of exposure with test substance of particle size of 4 micron (especially for aerosols) with not less than 25% being 1 micron should be provided. Effects on respiratory rate, findings of bronchial lavage fluid examination, histological examination of respiratory passages and lung tissue should be included along with the regular parameters of systemic toxicity studies or assessment of margin of safety.

(1.5) Allergenicity or Hypersensitivity. - Standard tests include guinea pig maximization test (GPMT) and local lymph node assay (LLNA) in mouse. Any one of the two may be done.

Notes: (i) Guinea pig maximization test. - The test is to be performed in two steps; first, determination of maximum non-irritant and minimum irritant doses, and second, the main test. The initial study will also have two components. To determine the intradermal induction dose, four dose levels should be tested by the same route in a batch of four male and four female animals (2 of each sex should be given Freund's adjuvant). The minimum irritant dose should be used for induction. Similarly, a topical minimum irritant dose should be determined for challenge. This should be established in two males and two females. A minimum of six male and six female animals per group should be used in the main study. One test and one control group should be used. It is preferable to have one more positive control group. Intradermal induction (day 1) coupled with topical challenge (day21) should be done. If there is no response, re-challenge should be done 7 to 30days after the primary challenge. Erythema and oedema (individual animal scores as well as maximization grading) should be used as evaluation criteria.

(ii) Local lymph node assay. - Mice used in this test should be of the same sex, either only males or only females. Drug treatment is to be given on ear skin. Three graded doses, the highest being maximum non-irritant dose plus vehicle control should be used. A minimum of 6 mice per group should be used. Test material should be applied on ear skin on three consecutive days and on day 5, the draining auricular lymph nodes should be dissected out 5 hours after i.v. H-thymidine or bromo-deoxy-uridine (BrdU). Increase in H-thymidine or BrdU incorporation should be used as the criterion for evaluation of results.

(1.6) Genotoxicity.— Genotoxic compounds, in the absence of other data, shall be presumed to be trans-species carcinogens, implying a hazard to humans. Such compounds need not be subjected to long term carcinogenicity studies. However, if such a drug is intended to be administered for chronic illnesses or otherwise over a long period of time - a chronic toxicity study (up to one year) may be necessary to detect early tumorigenic effects. Genotoxicity tests are in vitro and in vivo tests conducted to detect compounds which induce genetic damage directly or indirectly. These tests should enable a hazard identification with respect to damage to De-oxy Ribonucleic Acid (DNA) and its fixation.

The following standard test battery is generally expected to be conducted:

(i) A test for gene mutation in bacteria.

(ii) An in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an in vitro mouse lymphomatic assay.

(iii) An in vivo test for chromosomal damage using rodent haematopoietic cells. Other genotoxicity tests e.g. tests for measurement of De-oxy Ribonucleic Acid (DNA) adducts, De-oxy Ribonucleic Acid (DNA) strand breaks, De-oxy Ribonucleic Acid (DNA) repair or recombination serve as options in addition to the standard battery for further investigation of genotoxicity test results obtained in the standard battery. Only under extreme conditions in which one or more tests comprising the standard battery cannot be employed for technical reasons, alternative validated tests can serve as substitutes provided sufficient scientific justification should be provided to support the argument that a given standard battery test is not appropriate.

(iv) Both in-vitro and in-vivo studies should be done. In-vitro studies should include Ames Salmonella assay and chromosomal aberrations (CA) in cultured cells. In-vivo studies should include micronucleus assay (MNA) or chromosomal aberrations (CA) in rodent bone marrow. Data analysis of chromosomal aberrations (CA) should include analysis of “gaps”.

(v) Cytotoxic anticancer agents. - Genotoxicity data are not required before Phase I and II trials. But these studies should be completed before applying for Phase III trials.

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Notes: *Ames' Test (Reverse mutation assay in Salmonella):* S. typhimurium tester strains such as TA98, TA100, TA102, TA1535, TA97 or Escherichia coli WP2 uvrA or Escherichia coli WP2 uvrA (pKM101) should be used.

(vi) In-vitro exposure (with and without metabolic activation, S9 mix) should be done at a minimum of 5 log dose levels. "Solvent" and "positive" control should be used. Positive control may include 9-amino-acridine, 2-nitrofluorine, sodium azide and mitomycin C, respectively, in the tester strains mentioned above. Each set should consist of at least three replicates. A 2.5 fold (or more) increase in number of revertants in comparison to spontaneous revertants would be considered positive.

(vii) In-vitro cytogenetic assay. - The desired level of toxicity for in vitro cytogenetic tests using cell lines should be greater than 50% reduction in cell number or culture confluency. For lymphocyte cultures, an inhibition of mitotic index by greater than 50% is considered sufficient. It should be performed in Chinese Hamster Ovary (CHO) cells or on human lymphocyte in culture. In-vitro exposure (with and without metabolic activation, S9 mix) should be done using a minimum of 3 log doses. "Solvent" and "positive" control should be included. A positive control like Cyclophosphamide with metabolic activation and Mitomycin C for without metabolic activation should be used to give a reproducible and detectable increase clastogenic effect over the background which demonstrates the sensitivity of the test system. Each set should consist of at least three replicates. Increased number of aberrations in metaphase chromosomes should be used as the criteria for evaluation.

(viii) In-vivo micronucleus assay. - One rodent species (preferably mouse) is needed. Route of administration of test substance should be the same as intended for humans. Five animals per sex per dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. A positive control like mitomycin C or cyclophosphamide should be used. Dosing should be done on day one and two of study followed by sacrifice of animals six hours after the last injection. Bone marrow from both the femora should be taken out, flushed with fetal bovine serum (20 min.), pelletted and smeared on glass slides. Giemsa-May Gruenwald staining should be done and increased number of micronuclei in polychromatic erythrocytes (minimum 1000) should be used as the evaluation criteria.

(ix) In-vivo cytogenetic assay. - One rodent species (preferably rat) is to be used. Route of administration of test substance should be the same as intended for humans. Five animals/sex/dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. Positive control may include cyclophosphamide. Dosing should be done on day one followed by intra-peritoneal colchicine administration at 22 hours. Animals should be sacrificed two hours after colchicine administration. Bone marrow from both the femora should be taken out, flushed with hypotonic saline (20 minutes), pelletted and resuspended in Carnoy's fluid. Once again the cells should be pelletted and dropped on clean glass slides with a Pasteur pipette. Giemsa staining should be done and increased number of aberrations in metaphase chromosomes (minimum 100) should be used as the evaluation criteria.

(1.7) Carcinogenicity.- Carcinogenicity studies should be performed for all drugs that are expected to be clinically used for more than six months as well as for drugs used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. Carcinogenicity studies are also to be performed for drugs if there is concern about their carcinogenic potential emanating from previous demonstration of carcinogenic potential in the product class that is considered relevant to humans or where structure-activity relationship suggests carcinogenic risk or when there is evidence of preneoplastic lesions in repeated dose toxicity studies or when long-term tissue retention of parent compound or metabolites results in local tissue reactions or other pathophysiological responses. For pharmaceuticals developed to treat certain serious diseases, Central Licencing Authority may allow carcinogenicity testing to be conducted after marketing permission has been granted.

In instances where the life-expectancy in the indicated population is short (i.e., less than 2 - 3 years) no long-term carcinogenicity studies may be required. In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When such drugs are intended for adjuvant therapy in tumour free patients or for prolonged use in non-cancer indications, carcinogenicity studies may be needed. Completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical trials, unless there is special concern for the patient population.

Carcinogenicity studies should be done in a rodent species (preferably rat). Mouse may be employed only with proper scientific justification. The selected strain of animals should not have a very high or very low incidence of spontaneous tumors. 107

At least three dose levels should be used. The highest dose should be sub-lethal, and it should not reduce the life span of animals by more than 10% of expected normal. The lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, e.g. 2.5x; to make allowance for the sensitivity of the species. The intermediate dose to be placed logarithmically between the other two doses. An untreated control and (if indicated) a vehicle control group should be included. The drug should be administered seven days a week for a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Generally, the period of dosing should be 24 months for rats and 18 months for mice.

Observations should include macroscopic changes observed at autopsy and detailed histopathology of organs and tissues. Additional tests for carcinogenicity (short-term bioassays, neonatal mouse assay or tests employing transgenic animals) may also be done depending on their applicability on a case to case basis.

Note: Each dose group and concurrent control group not intended to be sacrificed early should contain at least 50 animals of each sex. A high dose satellite group for evaluation of pathology other than neoplasia should contain 20 animals of each sex while the satellite control group should contain10animals of each sex. Observation parameters should include signs of intoxication, effect on body weight, food intake, clinical chemistry parameters, hematology parameters, urine analysis, organ weights, gross pathology and detailed histopathology. Comprehensive descriptions of benign and malignant tumour development, time of their detection, site, dimensions, histological typing etc. should be given.

(1.8) Animal toxicity requirements for clinical trials and marketing of a new drug.

Systemic Toxicity Studies			
Route of administration	Duration of proposed human administration	Human Phase(s) for which study is proposed to be conducted	Long term toxicity requirements
Oral or Parenteral or Transdermal	Single dose or several doses in one day, up to 1 week	I, II, III	2 species; 2 weeks
	>1 week but upto 2 weeks	I, II, III	2 species; 2weeks
	Upto 2 weeks	Marketing permission	2 species; 4weeks
	>2 weeks but upto 4 weeks	I, II,III	2 species; equal to duration of human exposure
		Marketing permission	2 species; 12 weeks
	> 4 weeks but upto 12 weeks	I,II,III	2 species; equal to duration of human exposure
		Marketing permission	2 species; 24 weeks
	> 12 weeks but upto 24 weeks	I,II,III	2 species; equal to duration of human exposure
		Marketing permission	2 species; Rodent 24 weeks, non-rodent 36 weeks
	> 24 weeks	I,II,III	2 species; Rodent 24 weeks, non-rodent 36weeks

		Marketing permission	2 species; Rodent 24 weeks, non-rodent 36 weeks
Inhalation (general Anaesthetics, aerosols)	Up to 2 weeks	I, II, III	2 species; I month (Exposure time 3h/d, 5d/week)
	Up to 4 weeks	I, II, III	2 species; 12 weeks (Exposure time 6h/d, 5d/week)
	>14 weeks	I, II, III	2 sp; 24 weeks (Exposure time 6h/d, 5d/week)
Local Toxicity Studies			
Dermal	Up to 2 weeks	I, II	1 species; 4 weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks
Ocular or Optic or Nasal	Up to 2 weeks	I, II	1 species; 4 weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks
Vaginal or Rectal	Up to 2 weeks	I, II	1 species; 4weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks

Special Toxicity Studies
Male Fertility Study: Phase III in male volunteers or patients
Female Reproduction and Development Toxicity Studies:
Segment II studies in 2 species; Phase II, III involving female patients of child bearing age.
Segment I study; Phase III involving female patients of child-bearing age.
Segment III study; Phase III for drugs to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development.
Allergenicity or Hypersensitivity:
Phase I, II, III - when there is a cause of concern or for parenteral drugs (including dermal application)
Photo-allergy or dermal photo-toxicity:
Phase I, II, III - if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential.
Genotoxicity:
In-vitro studies – Phase I
Both in-vitro and in-vivo - Phase II, III
Carcinogenicity:
Phase III - when there is a cause for concern, or when the drug is to be used for more than 6 months.

Abbreviations: d -day; **h**-hour; **I**, **II**, **III** - Phase of clinical trial;

Note: (1) Animal toxicity data generated in other countries may be accepted and may not be asked to be repeated or duplicated in India on a case to case basis depending upon the quality of data and the credentials of the laboratory where such data has been generated.

(2) Requirements for fixed dose combinations are given in clause 4 of this Schedule.

(1.9) Number of animals required for repeated-dose toxicity studies

14 to 28 days					84 to 182 days			
Group	Rodent (Rat)		Non-rodent (Dog or Monkey)		Rodent (Rat)		Non-rodent (Dog or Monkey)	
	Male	Female	Male	Female	Male	Female	Male	Female
Control	6 to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6
Low dose	6 to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6
Intermediat e dose	6 to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6
High dose	6to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6

(1.10) Laboratory parameters to be included in toxicity studies:

Haematological parameters			
Haemoglobin	Total Red Blood Cell count	Haematocrit	Reticulocyte
Total White Blood Cell count	Differential White Blood Cell Count	Platelet count	Terminal Bone Marrow Examination
Erythrocyte sedimentation rate (ESR) (Non-rodents only)	General Blood Picture: A Special mention of abnormaland immature cells should be made		
Coagulation parameters (Non-rodents only): Bleeding Time, coagulation Time, prothrombin time, Activated partial Thromboplastin Time			
Urinalysis Parameters			
Colour	Appearance	Specific Gravity	24 hours urinary output
Reaction(pH)	Albumin	Sugar	Acetone
Bile pigments	Urobilinogen	Occult Blood	
Microscopic examination of urinary sediment			
Blood Biochemical parameters			
Glucose	Cholesterol	Triglycerides	High density lipoproteins (HDL) cholesterol (Non-rodents only)
Low density lipoproteins (LDL)	Bilirubin	Serum glutamic pyruvic transaminase (SGPT) (Alanine aminotransferase (ALT)	Serum glutamic oxaloacetic transaminase (SGOT)
Cholesterol(Non-rodents only) Aspartate aminotransferase (AST)			
Alkaline Phosphatase (ALP)	GGT (Non-rodents only)	Blood urea Nitrogen	Creatinine

Total proteins	Albumin	Globulin (Calculated values)	Sodium
Potassium	Phosphorus	Calcium	
Gross and Microscopic Pathology			
Brain*: Cerebrum, Cerebellum, Midbrain	(Spinal cord)	Eye	(Middle Ear)
Thyroid	(Parathyroid)	Spleen	Thymus
Adrenal*	(Pancreas)	(Trachea)	Lung*
Heart*	Aorta	Oesophagus	Stomach
Duodenum	Jejunum	Terminal ileum	Colon
(Rectum)	Liver*	Kidney*	Urinary bladder
Epididymis	Testis*	Ovary	Uterus*
Skin	Mammary gland	Mesenteric lymph node	Skeletal muscle

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* Organs marked with an asterisk should be weighed.

( ) Organs listed in parenthesis should be examined if indicated by the nature of the drug or observed effects.

Non-clinical toxicity testing and safety evaluation data of an Investigational New Drug (IND) needed for the conduct of different phases of clinical trials.

Note: Refer clause 2 of Second Schedule for essential features of study designs of the non-

clinical toxicity studies listed below.

For Phase I Clinical Trials:

Systemic Toxicity studies:-

(I) Single dose toxicitystudies

(II) Dose Ranging Studies

(III) Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Male fertility study:

In-vitro genotoxicity tests, -

Relevant local toxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure).

Allergenicity or Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application).

Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to anagent causing photosensitivity or the nature of action suggests such a potential).

For Phase II Clinical Trials: Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I trial, with appropriate references.

In case of an application for directly starting a Phase II trial - complete details of then on clinical safety data needed for obtaining the permission for Phase I trial, as per the list provided above must be submitted.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

In-vivo genotoxicity tests.

Segment II reproductive or developmental toxicity study (if female patients of child bearing age are going to be involved).

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For Phase III Clinical Trials: Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I and II trials, with appropriate references. In case of an application for directly initiating a Phase III trial - complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and II trials, as per the list provided above must be provided.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Reproductive or developmental toxicity studies

Segment I (if female patients of child bearing age are going to be involved), and Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development).

Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).

For Phase IV Clinical Trials: Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I, II and III trials, with appropriate references.

In case an application is made for initiating the Phase IV trial, complete details of the non-clinical safety data needed for obtaining the permissions for Phase I, II and III trials, as per the list provided above must be submitted.

Application of Good Laboratory Practices (GLP) -

The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

(2) The animal toxicology requirements as referred above should be viewed as general guidance for drug developments. Animal toxicology studies may be planned, designed and conducted as per the International Council of Harmonization (ICH) guidelines to promote safe, ethical development and availability of new drugs with reduced use of animals in accordance with the 3R (reduce/refine/replace) principles.

3. Animal Pharmacology.- *(1) General Principles***.-** Specific and general pharmacological studies should be conducted to support use of therapeutics in humans. In the early stages of drug development enough information may not be available to rationally select study design for safety assessment. In such a situation, a general approach to safety pharmacology studies can be applied. Safety pharmacology studies are studies that investigate potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range or above.

1.1 Specific pharmacological actions,- Specific pharmacological actions are those which demonstrate the therapeutic potential for humans.

The specific studies that should be conducted and their design will be different based on the individual properties and intended uses of investigational drug. Scientifically validated methods should be used. The use of new technologies and methodologies in accordance with sound scientific principles should be preferred.

1.2 General pharmacological actions,-

1.2.1 Essential safety pharmacology.- Safety pharmacology studies need to be conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range and above. These studies should be designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; to evaluate adverse pharmacodynamic or pathophysiological effects observed in toxicology or clinical studies; and to investigate the mechanism of the adverse pharmacodynamic effects observed or suspected. The aim of the essential safety pharmacology is to study the effects of the test drug on vital functions. Vital organ systems such as cardiovascular, respiratory and central nervous systems should be studied. Essential safety pharmacology studies may be excluded or supplemented based on scientific rationale. Also, the exclusion of certain tests or exploration(s) of certain organs, systems or functions should be scientifically justified.

1.2.1.1 Cardiovascular system: Effects of the investigational drug should be studied on blood pressure, heart rate, and the electrocardiogram. If possible in vitro, in vivo and/or ex vivo methods including electrophysiology should also be considered.

1.2.1.2 Central nervous system: Effects of the investigational drug should be studied on motor activity, behavioural changes, coordination, sensory and motor reflex responses and body temperature.

1.2.1.3 Respiratory system: Effects of the investigational drug on respiratory rate and other functions such as tidal volume and haemoglobin oxygen saturation should be studied.

1.3 Follow-up and supplemental safety pharmacology studies.- In addition to the essential safety pharmacological studies, additional supplemental and follow-up safety pharmacology studies may need to be conducted as appropriate. These depend on the pharmacological properties or chemical class of the test substance, and the data generated from safety pharmacology studies, clinical trials, pharmacovigilance, experimental in vitro or in vivo studies, or from literature reports.

1.3.1 Follow-up studies for essential safety pharmacology: Follow-up studies provide additional information or a better understanding than that provided by the essential safety pharmacology.

1.3.1.1 Cardiovascular system: These include ventricular contractility, vascular resistance and the effects of chemical mediators, their agonists and antagonists on the cardiovascular system.

1.3.1.2 Central nervous system: These include behavioural studies, learning and memory, electrophysiology studies, neurochemistry and ligand binding studies.

1.3.1.3 Respiratory system: These include airway resistance, compliance, pulmonary arterial pressure, blood gases and blood pH.

1.3.2 Supplemental safety pharmacology studies: These studies are required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety pharmacological studies and are a cause for concern.

1.3.2.1 Urinary system: These include urine volume, specific gravity, osmolality, pH, proteins, cytology and blood urea nitrogen, creatinine and plasma proteins estimation.

1.3.2.2 Autonomic nervous system: These include binding to receptors relevant for the autonomic nervous system, and functional response to agonist or antagonist responses in vivo or in vitro, and effects of direct stimulation of autonomic nerves and their effects on cardiovascular responses.

1.3.2.3 Gastrointestinal system: These include studies on gastric secretion, gastric pH measurement, gastric mucosal examination, bile secretion, gastric emptying time in vivo and ileocaecal contraction in vitro.

1.3.2.4 Other organ systems: Effects of the investigational drug on organ systems not investigated elsewhere should be assessed when there is a cause for concern. For example, dependency potential, skeletal muscle, immune and endocrine functions may be investigated.

1.4 Conditions under which safety pharmacology studies are not necessary: Safety pharmacology studies are usually not required for locally applied agents e.g. dermal or ocular, in cases when the pharmacology of the investigational drug is well known, and/or when systemic absorption from the site of application is low. Safety pharmacology testing is also not necessary, in the case of a new derivative having similar pharmacokinetics and pharmacodynamics.

1.5 Timing of safety pharmacology studies in relation to clinical development :

1.5.1 Prior to first administration in humans: The effects of an investigational drug on the vital functions listed in the essential safety pharmacology should be studied prior to first administration in humans. Any follow-up or supplemental studies identified, should be conducted if necessary, based on a cause for concern.

1.5.2 During clinical development: Additional investigations may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development.

1.5.3 Before applying for marketing approval: Follow-up and supplemental safety pharmacology studies should be assessed prior to approval unless not required, in which case this should be justified. Available information from toxicology studies addressing safety pharmacology endpoints or information from clinical studies can replace such studies.

1.6 Application of Good Laboratory Practices (GLP): The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

4. Fixed Dose Combinations (FDCs). - Fixed dose combinations refer to products containing one or more active ingredients used for a particular indication. Fixed Dose Combinations (FDCs) can be divided into the following groups and data required for approval for marketing is described below:

(a) The first group of Fixed Dose Combinations (FDCs) includes those in which one or more of the active ingredients is a new drug. For such Fixed Dose Combinations (FDCs) to be approved for marketing data to be submitted will be similar to data required for any new drug (including clinical trials).

(b) (i) The second group Fixed Dose Combinations (FDCs) includes those in which active ingredients already approved or marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. If clinical trials have been carried out with the Fixed Dose Combination (FDC) in other countries, reports of such trials should be submitted. If the Fixed Dose Combination (FDC) is marketed abroad, the regulatory status in other countries should be stated.

(ii) For marketing permission, appropriate chemical and pharmaceutical data will be submitted. In case such a combination is not marketed anywhere in the world but these drugs are already in use concomitantly (not as a Fixed Dose Combination (FDC) but individually) for the said claim, marketing permission may be granted based on chemical and pharmaceutical data. Data showing the stability of the proposed dosage form will also have to be submitted.

(iii) For any other such Fixed Dose Combinations (FDCs), clinical trials may be required. For obtaining permission to carry out clinical trials with such Fixed Dose Combinations (FDCs) a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (Lethal Dose 50 (LD 50)) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio.

(c) The third group of Fixed Dose Combinations (FDCs) includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such Fixed Dose Combinations (FDCs), the appropriate rationale including published reports (if any) should be submitted to obtain marketing permission. Permission will be granted depending upon the nature of the claim and data submitted.

(d) The fourth group of Fixed Dose Combination (FDC) includes those whose individual active ingredients (or drugs from the same class) have been widely used in a particular indications for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience. It will have to be demonstrated that the proposed dosage form is stable and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. No additional animal or human data are generally required for these Fixed Dose Combinations (FDCs), and marketing permission may be granted if the Fixed Dose Combination (FDC) has an acceptable rationale.

5. Stability Testing of New Drugs. - Stability testing is to be performed to provide evidence on how the quality of a drug substance or formulation varies with time under the influence of various environmental factors such as temperature, humidity and light, and to establish shelf life for the formulation and recommended storage conditions.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety or efficacy. In case of formulations the testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system).

Validated stability-indicating analytical procedures should be applied. For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance.

In general, a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen should be sufficient to cover storage, shipment and subsequent use.

Stress testing of the drug substance should be conducted to identify the likely degradation products, which in turn establish the degradation pathways, evaluate the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of formulation involved.

Stress testing may generally be carried out on a single batch of the drug substance. It should include the effect of temperatures), humidity where appropriate, oxidation, and photolysis on the drug substance.

Data should be provided for

(a) Photostability on at least one primary batch of the drug substance as well as the formulation, as the case may be; and

(b) the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.

Long-term testing should cover a minimum of six months duration if there is no significant change at any time during six months testing at accelerated storage condition or twelve months duration if there is significant changes in the six months accelerated stability testing on at least three primary batches of the drug substance or the formulation at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Accelerated testing should cover a minimum of six months duration at the time of submission.

In case of drug substances, the batches should be manufactured to a minimum of pilot scale by the same synthetic route and using a method of manufacture that simulates the final process to be used for production batches. In case of formulations, two of the three batches should be at least pilot scale and the third one may be smaller. 114

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specifications as that intended for marketing.

The stability studies for drug substances should be conducted either in the same container - closure system as proposed for storage and distribution or in a container - closure system that simulates the proposed final packaging. In case of formulations, the stability studies should be conducted in the final container - closure system proposed for marketing.

Stability testing of new drug substances and formulations:

(i)Study conditions for drug substances and formulations intended to be stored under general conditions

Study	*Study conditions*	*Duration of study*
Long-term	30°C ± 2° C/75% RH ± 5% RH	6 months or 12 months
Accelerated	40°C ± 2° C/75% RH ± 5% RH	6 months

(ii) If at any time during 6 months testing under the accelerated storage condition, such changes occur that cause the product to fail in complying with the prescribed standards, additional testing under an intermediate storage condition should be conducted and evaluated against significant change criteria.

(iii) Study conditions for drug substances and formulations intended to be stored in a refrigerator.

Study	*Study conditions*	*Duration of study*
Long-term	5°C ± 3° C	6 months or 12 months
Accelerated	25°C ± 2° C/60% RH ± 5%RH	6 months

(iv) Study conditions for drug substances and formulations intended to be stored in a freezer

Study	*Study conditions*	*Duration of study*
Study	Study conditions	Durations of study
Long-term	-20° C ± 5° C	6 months or 12 months

(v) Drug substances intended for storage below -20° C shall be treated on a case-by-case basis.

(vi) Stability testing of the formulations after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in- use period.

TABLE 1

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS OR IMPORT OR MANUFACTURE OF NEW DRUGS FOR SALE IN THE COUNTRY

1. Introduction: A brief description of the drug and the therapeutic class to which it belongs.

2. Chemical and pharmaceutical information

2.1. Information on active ingredients.- Drug information (Generic Name, Chemical Name or International Nonproprietary Names (INN))

2.2. Physicochemical data.-

(a) Chemical name and Structure

Empirical formula

Molecular weight

(b) Physical properties

Description

Solubility

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Rotation

Partition coefficient

Dissociation constant.

2.3. Analytical data

Elemental analysis

Mass spectrum

NMR spectra

IR spectra

UV spectra

Polymorphic identification.

2.4. Complete monograph specification including

Identification

Identity or quantification of impurities

Enantiomeric purity

Assay.

2.5. Validations

Assay method

Impurity estimation method

Residual solvent/other volatile impurities (OVI) estimation method.

2.6. Stability studies (for details refer clause 5 of this Schedule)

Final release specification

Reference standard characterization

Material safety data sheet.

2.7. Data on formulation

(i) Dosage form

(ii) Composition

(iii) Master manufacturing formula

(iv) Details of the formulation (including inactive ingredients)

(v) In process quality control check

(vi) Finished product specification

(vii) Excipient compatibility study

(viii) Validation of the analytical method

(ix) Comparative evaluation with international brand or approved Indian brands, if applicable.

(x) Pack presentation

(xi) Dissolution assay

(xii) Impurities

(xiii) Content uniformity pH

(xiv) Force degradation study

(xv) Stability evaluation in market intended pack at proposed storage conditions

(xvi) Packing specifications

(xvii) Process validation

When the application is for clinical trials only, the international non-proprietary name (INN) or generic name drug category, dosage form and data supporting stability in the intended container-closure system for the duration of the clinical trial (information covered in item numbers 2.1, 2.3, 2.6, 2.7) are required.

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3. Animal pharmacology (for details refer clause 3 of this Schedule)

3.1. Summary

3.2. Specific pharmacological actions

3.3. General pharmacological actions

3.4. Follow-up and supplemental safety pharmacology studies

3.5. Pharmacokinetics: absorption, distribution; metabolism; excretion

4. Animal toxicology (for details refer clause 2 of this Schedule)

4.1. General aspects

4.2. Systemic toxicity studies

4.3. Male fertility study

4.4. Female reproduction and developmental toxicity studies

4.5. Local toxicity

4.6. Allergenicity or Hypersensitivity

4.7. Genotoxicity

4.8. Carcinogenicity

Note: Where the data on animal toxicity as per the specifications of clause 2has been submitted and the same has been considered by the regulatory authority of the country which had earlier approved the drug, the animal toxicity studies shall not be required to be conducted in India except in cases where there are specific concerns recorded in writing.

5. Human or Clinical pharmacology (Phase I)

5.1. Summary

5.2. Specific Pharmacological effects

5.3. General Pharmacological effects

5.4. Pharmacokinetics, absorption, distribution, metabolism, excretion

5.5. Pharmacodynamics / early measurement of drug activity

6. Therapeutic exploratory trials (Phase II)

6.1. Summary

6.2. Study report as given in Table 6 of Third Schedule

7. Therapeutic confirmatory trials (Phase III)

7.1. Summary

7.2. Individual study reports with listing of sites and investigators.

8. Special studies

8.1. Summary

8.2. Bio-availability or Bio-equivalence.

8.3. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

9. Regulatory status in other countries

9.1. Countries where the drug is

(a) Marketed

(b) Approved

(c) Approved as Investigational New Drug (IND)

(d) Withdrawn, if any, with reasons

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9.2. Restrictions on use, if any, in countries where marketed/approved

9.3. Free sale certificate or certificate of analysis, as appropriate.

10. Prescribing information

10.1. Proposed full prescribing information
10.2. Drafts of labels and cartons

11. Samples and Testing protocol/s

11.1. Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Central Licencing Authority), with testing protocols, full impurity profile and release specifications.

12. New chemical entity and Global clinical trial:

12.1Assessment of risk versus benefit to the patients
12.2Innovation vis-à-vis existing therapeutic option
12.3 Unmet medical need in the country.

13. Copy of license to manufacture any drug for sale granted by State Licencing Authority (in case the application is for manufacture for sale of new drug)

Note: (1) All items may not be applicable to all drugs. For explanation, refer text of this First Schedule, Second Schedule and Third Schedule.

(2) For requirements of data to be submitted with application for clinical trials refer text of the First Schedule, Second Schedule and Third Schedule.

TABLE 2
DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF PERMISSION TO IMPORT OR MANUFACTURE A NEW DRUG

ALREADY APPROVED IN THE COUNTRY

1. Introduction

A brief description of the drug and the therapeutic class

2. Chemical and pharmaceutical information

2.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

2.2 Dosage form and its composition

2.3 Test specifications

(a) active ingredients

(b) inactive ingredients

2.4 Tests for identification of the active ingredients and method of its assay

2.5 Specifications of finished product

2.6 Outline of the method of manufacture of active ingredient and finished product

2.7 Stability data

3. Marketing information

3.1 Proposed package insert or promotional literature

3.2 Draft specimen of the label and carton

4. Special studies conducted with approval of Central Licencing Authority

4.1 Bioavailability or Bioequivalence and comparative dissolution studies for oral dosage forms

4.2 Sub-acute animal toxicity studies for intravenous infusions and injectables.

TABLE 3

DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR CONDUCT OF CLINICAL TRIAL OF AN APPROVED NEW DRUG WITH NEW CLAIMS, NAMELY, NEW INDICATION OR NEW DOSAGE FORM OR NEW ROUTE OF ADMINISTRATION OR NEW STRENGTH OR TO IMPORT OR MANUFACTURE SUCH NEW DRUG FOR SALE OR DISTRIBUTION

1. Number and date of permission or license already granted for the approved new drug.
2. Therapeutic justification for new claim- new indication or modified dosage form/new route of administration

Chemical and Pharmaceutical information

3.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

3.2 Dosage form and its composition

3.3 Test specifications

(a) active ingredients

(b) inactive ingredients

3.4 Tests for identification of the active ingredients and method of its assay

3.5 Specifications of finished product

3.6 Outline of the method of manufacture of active ingredient and finished product

3.7 Stability data

4. Therapeutic justification for new claim or modified dosage form
5. Animal pharmacological and toxicological data as referred in clause 1, clause 2 and clause 3 of this Schedule.
6. Clinical trial data as referred in clause 1 of this Schedule.
7. Regulatory status in other countries
8. Marketing information:

8.1 Proposed package insert or promotional literature

8.2 Draft specimen of the label and carton

TABLE 4

DATA TO BE SUBMITTED ALONG WITH APPLICATION TO CONDUCT CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF A PHYTOPHARMACEUTICAL DRUG IN THE COUNTRY

PART – A

1. Data to be submitted by the applicant:

1.1.A brief description or summary of the phyto pharmaceutical drug giving the botanical name of the plant (including vernacular or scriptural name, wherever applicable), formulation and route of administration, dosages, therapeutic class for which it is indicated and the claims to be made for the phytopharmaceutical product.

1.2.Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethno medicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.

1.3.Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine literature or reports on current usage of the formulation.

1.4.Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed,-

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

1.5.Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years wherever applicable.

1.6.Present usage of the phytopharmaceutical drug - to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

2. Human or clinical pharmacology information:

2.1.Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed,-

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

2.2. Pharmacodynamic information (if available).

2.3.Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with English translation to be attached.)

PART - B

DATA GENERATED BY APPLICANT

3. Identification, authentication and source of plant used for extraction and fractionation:

3.1 Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.

3.2 Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. (Furnish certificate of confirmation of botanical identity by a qualified taxonomist).

3.3 Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.

3.4 Season or time of collection.

3.5 Source of the plant including its geographical location and season or time of collection.

3.6 A statement indicating whether the species is any of the following, namely:-

(a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered species (CITES) of wild Fauna and Flora;

(b) entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);

(c) any known genotypic, chemotypic and ecotypic variability of species.

3.7. A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely: -

(a) harvest location;

(b) growth conditions;

(c) stage of plant growth at harvest;

(d) harvesting time;

(e) collection, washing, drying and storage conditions;

(f) handling, garbling and transportation;

(g) grinding, pulverising of the plant material; and

(h) sieving for getting uniform particle size of powdered plant material.

3.8. Quality specifications, namely:-

(a) foreign matter;

(b) total ash;

(c) acid insoluble ash;

(d) pesticide residue;

(e) heavy metal contamination;

(f) microbialload;

(g) chromatographic finger print profile with phytochemical reference marker;

(h) assay for bio-active or phytochemical compounds; and

(i) chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).

3.9 An undertaking to supply specimen sample of plant duly labelled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.

4. Process for extraction and subsequent fractionation and purification:

4.1. Quality specifications and test methods for starting material.

4.2. Steps involved in processing.

(a) details of solvent used, extractive values, solvent residue tests or limits,

physico-chemical tests, microbial loads, heavy metal contaminants, chromatographic finger print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;

(b) characterisation of final purified fraction;

(c) data on bio-active constituent of final purified fraction;

(d) information on any excipients or diluents or stabiliser or preservative used, if any.

4.3. Details of packaging of the purified and characterised final product, storage conditions and labelling.

5. Formulation of phytopharmaceutical drug applied for:

5.1. Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per unit dose, name and proportions of all excipients, stabilisers and any other agent used and packaging materials.

5.2. Test for identification for the phytopharmaceutical drug.

5.3.Quality specifications for active and inactive phytopharmaceutical chromatographic finger print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.

6. Manufacturing process of formulation:

6.1.The outline of the method of manufacture of the dosage form, along with environmental controls, in-process quality control tests and limits for acceptance.

6.2.Details of all packaging materials used, packing steps and description of the final packs.

6.3.Finished product's quality specifications, including tests specific for the dosage form, quality and chromatographic finger print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.

7. Stability data:

7.1. Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature or 40+/- 2 deg. C and humidity at 75%RH +/-5%RHfor 0, 1, 2, 3 and 6 months.

7.2 Stability data of the phytopharmaceutical drug in dosage form or formulation stored at room temperature or 40 +/- 2 deg. C and humidity at 75%RH +/-5%RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.

8. Safety and pharmacological information:

8.1. Data on safety and pharmacological studies to be provided.

8.2. Animal toxicity and safety data:

(a) 28 to 90 days repeat dose oral toxicity on two species of animals;

(b) In-vitro genotoxicity data (Ame's test and Chromosomal aberration test);

(c) dermal toxicity tests for topical use products;

(d) teratogenicity study (only if phytopharmaceutical drug is intended for use during pregnancy).

9. Human studies:

9.1.Clinical trials for phytopharmaceutical drugs to be conducted as per applicable Rules and guidelines for new drugs.

9.2.For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.

9.3.Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies:

Provided that in the case of phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.

10. Confirmatory clinical trials:

10.1. Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.

10.2. Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable Rules and guidelines.

10.3. Submit information on how the quality of the formulation would be maintained during the above studies.

11. Regulatory status:

11.1. Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as Traditional medicine or as an approved drug.

12. Marketing information:

12.1. Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.

12.2. Draft of the text for label and carton.

13. Post marketing surveillance(PMS):

13.1. The applicant shall furnish periodic safety update reports every six months for the first two years after approval the drug is granted.

13.2. For subsequent two years the periodic safety update reports need to be submitted annually.

14. Any other relevant information:

Any other relevant information which the applicant considers that it will help in scientific evaluation of the application.

THIRD SCHEDULE

(See rules 8, 10, 11, 25, 35, 42 and 49)

CONDUCT OF CLINICAL TRIAL

1. Conduct of clinical trial.-

(i) Clinical trial shall be conducted in accordance with the provisions of the Act and these Rules and principles of Good Clinical Practice Guidelines.

(ii) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Central Licencing Authority and the approval obtained from the respective ethics committee.

(iii)The Central Licencing Authority shall be informed of the approval of the respective institutional ethics committee in accordance with these rules.

(iv) All trial investigator should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified physician (or dentist, when appropriate) who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. Laboratories used for generating data for clinical trials should be compliant with good laboratory practices.

(v) Protocol amendments, if become necessary before initiation or during the course of a clinical trial, all such amendments should be submitted to the Central Licencing Authority in writing along with the approval by the ethics committee, if available, which has granted the approval for the study.

(vi) No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and Central Licencing Authority except when it is necessary to eliminate immediate hazards to the trial subject or when change involves only logistic or administrative or minor aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Central Licencing Authority. Administrative or logistic changes or minor amendments in the protocol should be notified to the Central Licencing Authority within thirty days.

2. Informed Consent.–

(a) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is nontechnical and understandable by the study subject.

(b) The subject's consent must be obtained in writing using an "Informed Consent Form". Both the patient information sheet as well as the informed consent form should have been approved by the ethics committee and furnished to the Central Licencing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Central Licencing Authority before such changes are implemented.

(c) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative a legally acceptable representative is a person who is able to give consent for or authorise and intervention in the patient as provided by the law of India).

(d) If the trial subject his or her legally acceptable representative is unable to read or write an impartial witness should be present during the entire informed consent process who must append his or her signature to the consent form.

(e) In case of clinical trials on paediatrics, the subjects are legally unable to provide written informed consent, and are dependent on their parent or legal guardian to assume responsibility for their participation in clinical studies. In such case,-

(i) Written informed consent should be obtained from the parent or legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand.

(ii) Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form.

(iii)Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent or legal guardian, the welfare of a paediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental or legal guardian consent should be sufficient to allow participation in the study.

(f) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the informed consent form for trial subject is given in Table 3of this Schedule.

(g) An audio-video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record:

Provided that in case of clinical trial of anti-HIV and anti-leprosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.

3.Responsibilities. -

(1) Sponsor.- (i) The clinical trial sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practices Guidelines as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with Good Clinical Practices Guidelines and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Central Licencing Authority at the prescribed periodicity.

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(iii) In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions, if any, and the reason for discontinuation of the study or non-pursuit of the new drug application;

(iv)Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Central Licencing Authority, the Chairperson of the ethics committee and the head of the institution where the trial has been conducted, within fourteen days of knowledge of occurrence of the serious adverse event as specified in Table 5 of this Schedule;

(v) In case of injury or death occurring to the trial subject, the sponsor (whether a pharmaceutical company or an institution) or his representative or the investigator or the institution or centre where the study was conducted, as the case may be, shall make payment for medical management of the subject and also provide financial compensation for the clinical trial related injury or death in accordance with the procedure as prescribed in Chapter VI of these rules

(vi)The sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical trial, shall submit details of compensation provided or paid for clinical trial related injury or death, to the Central Licencing Authority thirty days of the receipt of the order of the Central Licencing Authority.

(vii) The sponsor shall provide post-trial access of the investigational drug by giving the drug free of cost to the trial subject as per directions of the Central Licencing Authority in special circumstances on the recommendations of the investigator and the ethics committee and written consent of the patient in accordance with rule 27.

(2) Investigator.- (i) The investigator shall be responsible for the conduct of the trial according to the protocol and the Good Clinical Practices Guidelines and also for compliance as per the undertaking given in Table 4. Standard operating procedures are required to be documented by the investigators for the tasks performed by them.

(i) During and following a subject's participation in trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events.

(ii) Investigator shall report all serious adverse events to the Central Licencing Authority, the sponsor or his representative, whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical trial, and the ethics committee that accorded approval to the study protocol, within twenty-four hours of their occurrence.

(iv) In case, the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the investigator to the Central Licencing Authority, the Chairperson of the ethics committee and the Head of the institution where the trial has been conducted within fourteen days of the occurrence of the serious adverse event.

(v) The investigator shall provide information to the trial subject through informed consent process as provided in Table 3about the essential elements of the clinical trial and the subject's right to claim compensation in case of trial related injury or death. He shall also inform the subject his or her nominee of their rights to contact the sponsor or his representative whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical trial for the purpose of making claims in the case of trial related injury or death.

(3) Ethics committee.-

(i) It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well-being of all trial subjects.

(ii) The ethics committee should exercise particular care to protect the rights, safety and well-being of all vulnerable subjects participating in the study, e.g., members of a group with hierarchical structure (e.g. prisoners armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or other incapable of personally giving consent.

(iii) Ethics committee should get documented "standard operating procedures' and should maintain a record of its proceedings.

(iv) Ethics committee should make, at appropriate intervals, an ongoing review of the trials for which they have reviewed the protocol. Such a review may be based on the periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or visiting the study sites.

(v) In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the Investigator as well as to the Central Licencing Authority.

(vi) In case of serious adverse event occurring to the trial subject, the ethics committee shall forward its report or order on the event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the sponsor or his representative or institution or centre, as the case may be, in accordance with Chapter VI of these rules.

TABLE 1

INFORMATION TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF REGISTRATION OF ETHICS COMMITTEE AND FORMAT FOR ACCORDING APPROVAL

(A) Information required to be submitted by the applicant for registration of ethics committee:

(a) Name of the ethics committee.

(b) Authority under which the ethics committee has been constituted, membership requirements, the term of reference, conditions of appointment and the quorum required.

(c) The procedure for resignation, replacement or removal of members.

(d) Address of the office of the ethics committee.

(e) Name, address, qualification, organisational title, telephone number, fax number, email, mailing address and brief profile of the Chairperson.

(f) Names, qualifications, organisational title, telephone number, fax number, e-mail and mailing address of the members of the ethics committee. The information shall also include member's specialty (primary, scientific or non-scientific), member's affiliation with institutions and patient group representation, if any.

(g) Details of the supporting staff.

(h) The standard operating procedures to be followed by the committee in general.

(i) Standard operating procedures to be followed by the committee for vulnerable population

(j) Policy regarding training for new and existing committee members along with standard operating procedures.

(k) Policy to monitor or prevent the conflict of interest along with standard operating procedures.

(l) If the committee has been audited or inspected before, give details.

(B) Format for according approval to clinical trial protocol by the ethics committee

To

Dr.

Dear Dr._____

The Institutional ethics committee or independent ethics committee (state name of the committee, as appropriate) reviewed and discussed your application to conduct the clinical trial entitled "…….. "on…….(date).
The following documents were reviewed:

(a) Trial protocol (including protocol amendments), dated…….version No.(s) ……

(b) Patient information sheet and informed consent form (including updates, if any) in English or vernacular language.

(c) Investigator's brochure, dated..... , Version no…… Proposed methods for patient accrual including advertisements etc. proposed to be used for the purpose.

(d) Principal investigator's current Curriculum Vitae.

(e) Insurance policy or compensation for participation and for serious adverse events occurring during the study participation.

(f) Investigator's agreement with the sponsor.

(g) Investigator's undertaking (Table 4).

The following members of the ethics committee were present at the meeting held on (date, time, place).

……Chairperson of the ethics committee;

…….Member-Secretary of the ethics committee;

…….Name of each member with designation;

We approve the trial to be conducted in its presented form.

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The ethics committee to be informed about the progress of the study, any Serious Adverse Events (SAE) occurring in the course of the study, any changes in the protocol and patient information or informed consent and to be provided with a copy of the final report.

Yours sincerely,

Member Secretary, Ethics Committee

TABLE 2

CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL TRIALS

Title Page

(a) Full title of the clinical study,

(b) Protocol, Study number, and protocol version number with date.

(c) The Investigational New Drug (IND) name/number of the investigational drug.

(d) Complete name and address of the Sponsor and contract research organization if any. (e) List of the investigators who are conducting the study, their respective institutional

affiliations and site locations

(f) Name of clinical laboratories and other departments and/or facilities participating in thestudy.

Table of Contents

1. Background and introduction

(a) Preclinical experience

(b) Clinical experience

Previous clinical work with the new drug should be reviewed here and a description of how the current protocol extends existing data should be provided. If this is an entirely new indication, how this drug was considered for this should be discussed. Relevant information regarding pharmacological, toxicological and other biological properties of the drug/biologic/medical device, and previous efficacy and safety experience should be described.

2. Study rationale: This section should describe a brief summary of the background information relevant to the study design and protocol methodology. The reasons for performing this study in the particular population included by the protocol should be provided.

3. Study objective (primary as well as secondary) and their logical relation to the study design.

4. Study design-

(a) Overview of the study design: Including a description of the type of study (i.e., double-blind, multicentre, placebo controlled, etc.), a detail of the specific treatment groups and number of study Subjects in each group and investigative site, Subject number assignment, and the type, sequence and duration of study periods.

(b) Flow chart of the study

(c) A brief description of the methods and procedures to be used during the study.

(d) Discussion of study design: This discussion details the rationale for the design chosen for this study.

5. Study population: the number of subjects required to be enrolled in the study at the investigative site and by all sites along with a brief description of the nature of the subject population required is also mentioned.

6. Subject eligibility

(a) Inclusion criteria

(b) Exclusion criteria

7. Study assessments - plan, procedures and methods to be described in detail.

8. Study conduct stating the types of study activities that would be included in this section would be: medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom measurement, dispensation and retrieval of medication, Subject cohort assignment, adverse event review, etc.

Each visit should be described separately as Visit 1, Visit 2, etc.

Discontinued subjects: Describes the circumstances for Subject withdrawal, dropouts, or other reasons for discontinuation of Subjects. State how drop outs would be managed and if they would be replaced describe the method of handling of protocol waivers, if any. The person who approves all such waivers should be identified and the criteria used for specific waivers should be provided.

Describes how protocol violations will be treated, including conditions where the study will be terminated for noncompliance with the protocol.

9. Study treatment-

(a) Dosing schedule (dose, frequency, and duration of the experimental treatment) Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency, and duration of concomitant treatment should be stated.

(b) Study drug supplies and administration: A statement about who is going to provide the study medication and that the investigational drug formulation has been manufactured following all regulations Details of the product stability, storage requirements and dispensing requirements should be provided.

(c) Dose modification for study drug toxicity: Rules for changing the dose or stopping the study drug should be provided.

(d) Possible drug interactions

(e) Concomitant therapy: The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a Subject is not allowed to use during parts of or the entire study. If any washout periods for prohibited medications are needed prior to enrolment, these should be described here.

(f) Blinding procedures: A detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the Subject

(g) Un-blinding procedures: If the study is blinded, the circumstances in which un-blinding may be done and the mechanism to be used for un-blinding should be given

10. Adverse Events:

Description of expected adverse events should be given.

Procedures used to evaluate an adverse event should be described.

11. Ethical considerations: Give the summary of:

(a) Risk/benefit assessment:

(b) Ethics committee review and communications

(c) Informed consent process

(d) Statement of subject confidentiality including ownership of data and coding procedures.

12. Study monitoring and supervision:

A description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected to perform monitoring.

Case Record Form (CRF) completion requirements, including who gets which copies of the forms and any specific required in filling out the forms Case Record Form correction requirements, including who is authorized to make corrections on the Case Record Form and how queries about study data are handled and how errors, if any, are to be corrected should be stated.

Investigator study files, including what needs to be stored following study completion should be described.

13. Investigational Product Management:

(a) Give investigational product description and packaging (stating all ingredients and the formulation of the investigational drug and any placebos used in the study)

(b) The precise dosing required during the study

(c) Method of packaging, labelling, and blinding of study substances

(d) Method of assigning treatments to subjects and the subject identification code numbering system

(e) Storage conditions for study substances

(f) Investigational product accountability: Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed, and returned or destroyed.

(g) Describe policy and procedure for handling unused investigational products.

14. Data Analysis: Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.

Statistical analysis: Give complete details of how the results will be analysed and reported along with the description of statistical tests to be used to analyse the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data; method of evaluation of the data for treatment failures, non-compliance, and Subject withdrawals; rationale and conditions for any interim analysis if planned.

Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable.

15. Undertaking by the Investigator (see Table 4)

16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); Case Record Form (CRF) and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

TABLE 3

INFORMED CONSENT

1. Checklist of informed consent documents for clinical trial subject,-

1.1 Essential elements:

(i) Statement that the study involves research and explanation of the purpose of the research.

(ii) Expected duration of the participation of subject.

(iii) Description of the procedures to be followed, including all invasive procedures.

(iv) Description of any reasonably foreseeable risks or discomforts to the Subject.

(v) Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.

(vi) Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

(vii) Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records.

(viii) Trial treatment schedule and the probability for random assignment to each treatment (for randomized trials).

(ix) Statement describing the financial compensation and the medical management as under:

(a) In case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.

(b) In the event of a trial related injury or death, the sponsor or his representative or the investigator or centre, as the case may be, in accordance with the rule 39, as the case may be, shall provide financial compensation for the injury or death.

(x)An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury.

(xi) The anticipated prorated payment, if any, to the subject for participating in the trial.

(xii) Responsibilities of subject on participation in the trial.

(xiii) Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled.

(xiv) Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

(xv) Statement that in the case of placebo controlled trial, the placebo administered to the subjects shall not have any therapeutic effect.

(xvi) Any other pertinent information.

1.2 Additional elements, which may be required:

(a) Statement of foreseeable circumstances under which the participation of the subject may be terminated by the Investigator without his or her consent.

(b) Additional costs to the subject that may result from participation in the study.

(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

(d) (d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.

(e). A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or foetus, if the Subject is or may become pregnant), which are currently unforeseeable.

(f) Approximate number of Subjects enrolled in the study.

2. Format of informed consent form for Subjects participating in a clinical trial –

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name:_____

Date of Birth/Age: _____

Address of the Subject ___

Qualification _____

Occupation: Student or Self-Employed or Service or Housewife or Others (Please click as appropriate) .

Annual Income of the subject:

Name and address of the nominees and his relation to the subject (for the purpose of compensation in case of trial related death).

		Place Initial box (Subject)
(i)	I confirm that I have read and understood the information Sheet dated _____ for the above study and have had the opportunity to ask questions.	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
(iii)	I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes	[ ]
(v)	I agree to take part in the above study.	[ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

Date: _____/ ____ /

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Signatory's Name: _____

Signature of the Investigator: _____ Date: ____ / ____ /

Study Investigator's Name: ___ _____

Signature of the Witness_____ Date: ____ / ____ /

Name of the Witness:_____

Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the subject his or her attendant.

TABLE 4

UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator (or Investigators when there is no Principal Investigator).
2. Name and address of the medical college, hospital or other facility where the clinical trial will be conducted: Education, training & experience that qualify the Investigator for the clinical trial (Attach details including Medical Council registration number, or any other statements of qualifications)
3. Name and address of all clinical laboratory facilities to be used in the study.
4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.
5. Names of the other members of the research team (Co-or sub-Investigators) who will be assisting the Investigator in the conduct of the investigations.
6. Protocol Title and Study number (if any) of the clinical trial to be conducted by the Investigator.
7. Commitments:

(i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary ethics committee and regulatory approvals have been obtained.

(ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval or favourable opinion from the ethics committee of the amendment, except where necessary to eliminate an immediate hazard to the trial subject or when the changes involved are only logistical or administrative in nature.

(iii) I agree to personally conduct or supervise the clinical trial at my site.

(iv) I agree to inform all trial subject, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the New Drugs and Clinical Trials Rules, 2019 and Good Clinical Practices guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory requirements and Good Clinical Practices guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit or inspection by the Sponsor, ethics committee, Central Licencing Authority or their authorised representatives, in accordance with regulatory provisions and the Good Clinical Practices guidelines. I will fully cooperate with any study related audit conducted by regulatory officials or authorised representatives of the Sponsor.

(ix) I agree to promptly report to the ethics committee all changes in the clinical trial activities and all unanticipated problems involving risks to human subjects or others.

(x) I agree to inform all serious adverse events to the Central Licencing Authority, sponsor as well as the ethics committee within twenty-four hours of their occurrence. In case, of failure to do so, I shall furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

(xi) The report of the serious adverse event, after due analysis, shall also be forwarded by me to the Central Licencing Authority, the Chairperson of the ethics committee and the Head of the institution where the trial has been conducted within fourteen days in accordance with the regulatory requirements. 130

(xii) I will maintain confidentiality of the identification of all participating subjects and assure security and confidentiality of study data.

(xiii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials.

8. Signature of Investigator with date.

TABLE 5

DATA ELEMENTS FOR REPORTING SERIOUS ADVERSE EVENTS OCCURRING IN A CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

1. Patient Details:

Initials and other relevant identifier (hospital or out-patient department (OPD) record number etc)*

Gender

Age or date of birth

Weight

Height

2. Suspected Drug(s) :

Generic name of the drug*

Indication(s) for which suspect drug was prescribed or tested.

Dosage form and strength.

Daily dose and regimen (specify units - e.g., mg, ml, mg/kg).

Route of administration.

Starting date and time of day.

Stopping date and time, or duration of treatment

3. Other Treatment(s):

Provide the same information for concomitant drugs (including non-prescription or Over the Counter OTC drugs) and non-drug therapies, as for the suspected drug(s).

4. Details of Serious Adverse Event :

Full description of the event including body site and severity, as well as the criterion (or criteria) for considering the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the event*

Start date (and time) of onset of event.

Stop date (and time) or duration of event.

Dechallenge and rechallenge information.

Setting (e.g., hospital, out-patient clinic, home, nursing home).

5. Outcome

Information on recovery and any sequelae; results of specific tests or treatment that may have been conducted.

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected event; Any post-mortem findings.

Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.

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6. Details about the Investigator*

Name and Address

Telephone number

Profession (specialty)

Date of reporting the event to Central Licencing Authority:

Date of reporting the event to ethics committee overseeing the site:

Signature of the Investigator or Sponsor

Note: Information marked * must be provided.

TABLE 6

STRUCTURE, CONTENT AND FORMAT FOR CLINICAL TRIAL REPORT

1. Title Page: This page should contain information about the title of the study, the protocol code, name of the investigational product tested, development Phase, indication studied, a brief description of the trial design, the start and end date of patient accrual and the names of the Sponsor and the participating Institutes (Investigators).

2. Study Synopsis (1 to 2 pages): A brief overview of the study from the protocol development to the trial closure should be given here. This section will only summarise the important conclusions derived from the study.

3. Statement of compliance with the Good Clinical Practices Guidelines.

4. List of abbreviations and definitions

5. Table of contents

6. Ethics Committee: This section should document that the study was conducted in accordance with the ethical principles of Declaration of Helsinki. A detailed description of the Ethics Committee constitution and dates of approvals of trial documents for each of the participating sites should be provided. A declaration should state that Ethics Committee (EC) notifications as per Good Clinical Practice Guidelines and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research have been followed.

7. Study Team: Briefly describe the administrative structure of the study (Investigators, site staff, Sponsor or designates, Central laboratory etc.).

8. Introduction: A brief description of the product development rationale should be given here.

9. Study Objective: A statement describing the overall purpose of the study and the primary and secondary objectives to be achieved should be mentioned here.

10. Investigational Plan: This section should describe the overall trial design, the Subject selection criteria, the treatment procedures, blinding or randomisation techniques if any, allowed or disallowed concomitant treatment, the efficacy and safety criteria assessed, the data quality assurance procedures and the statistical methods planned for the analysis of the data obtained.

11. Trial Subjects: A clear accounting of all trial Subjects who entered the study will be given here. Mention should also be made of all cases that were dropouts or protocol deviations. Enumerate the patients screened, randomised, and prematurely discontinued. State reasons for premature discontinuation of therapy in each applicable case.

12. Efficacy evaluation: The results of evaluation of all the efficacy variables will be described in this section with appropriate tabular and graphical representation. A brief description of the demographic characteristics of the trial patients should also be provided along with a listing of patients and observations excluded from efficacy analysis.

13. Safety Evaluation: This section should include the complete list

13.1 all serious adverse events, whether expected or unexpected and

13.2 unexpected adverse events whether serious or not (compiled from data received as per Table 5 of this Schedule).

The comparison of adverse events across study groups may be presented in a tabular or graphical form. This section should also give a brief narrative of all important events considered related to the investigational product.

14 Discussion and overall Conclusion: Discussion of the important conclusions derived from the trial and scope for further development.

15. List of References:

16. Appendices: List of Appendices to the Clinical Study Report

(a) Protocol and amendments

(b) Specimen of Case Record Form

(c) Investigators' names with contact addresses, phone, e-mail etc.

(d) Patient data listings

(e) List of trial participants treated with investigational product

(f) Discontinued participants

(g) Protocol deviations

(h) Case Record Forms of cases involving death and life threatening adverse event cases

(i) Publications from the trial

(j) Important publications referenced in the study

(k) Audit certificate, if available

(l) Investigator' certificate that he/she has read the report and that the report accurately describes the conduct and the results of the study.

TABLE 7

INVESTIGATOR'S BROCHURE

The Investigator's Brochure should contain the version number, release date along with the following sections, each with literature references where appropriate:

1 Table of Contents

2 Summary: A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

3 Introduction: A brief introductory statement should be provided that contains the chemical name (and generic and trade name when approved) of the investigational product, all active ingredients, the investigational product pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product, and the anticipated prophylactic, therapeutic, or diagnostic indication. Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

4 Physical, Chemical, and Pharmaceutical Properties and Formulation: A description should be provided of the investigational product substance (including the chemical or structural formula), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form should also be given. Any structural similarities to other known compounds should be mentioned.

5 Nonclinical Studies

5.1 Introduction: The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in human. The information provided may include the following, as appropriate, if known or available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution

- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format or listings should be used whenever possible to enhance the clarity of the presentation. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology: A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals: A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology: A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitization)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

6 Effects in Humans: (a) A thorough discussion of the known effects of the investigational products in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational products other than from in clinical trials, such as from experience during marketing.

(b) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational products should be presented, including the following, if available:

- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(c) Safety and Efficacy: A summary of information should be provided about the investigational product's or products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of

summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidence across indications or subgroups should be discussed. The Investigators Brochure IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the products.

(d) Marketing Experience: The Investigator's Brochure should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The Investigator's Brochure should also identify all the countries where the investigational product did not receive approval or registration for marketing or was withdrawn from marketing or registration.

7 Summary of Data and Guidance for the Investigator: This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational products, wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials. The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational products. Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug a reaction that is based on previous human experience and on the pharmacology of the investigational product.

TABLE 8

PRESCRIBING INFORMATION

1. Generic Name
2. Qualitative and quantitative composition
3. Dosage form and strength
4. Clinical particulars
   - 4.1 Therapeutic indication
   - 4.2 Posology and method of administration
   - 4.3 Contraindications
   - 4.4 Special warnings and precautions for use
   - 4.5 Drugs interactions
   - 4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
   - 4.7 Effects on ability to drive and use machines
   - 4.8 Undesirable effects
   - 4.9 Overdose
5. Pharmacological properties
   - 5.1 Mechanism of Action
   - 5.2Pharmacodynamicproperties
   - 5.3 Pharmacokinetic properties
6. Nonclinical properties
   - 6.1 Animal Toxicology or Pharmacology
7. Description
8. Pharmaceutical particulars
   - 8.1 Incompatibilities
   - 8.2 Shelf-life

8.3 Packaging information

8.4 Storage and handing instructions

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9. Patient Counselling Information

10. Details of manufacturer

11. Details of permission or licence number with date

12. Date of revision

FOURTH SCHEDULE

(See rules 33, 45, 48, 49 and 52)

REQUIREMENTS AND GUIDELINES FOR CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF NEW DRUGS OR INVESTIGATIONAL

NEW DRUGS

1. General Principles: (1) Bioavailability or Bioequivalence focus on the release of an active drug from its dosage form and subsequent absorption into the systemic circulation. Bioavailability or Bioequivalence study of a pharmaceutical formulation is one of the components to ensure efficacy and safety of pharmaceutical product.

(2) Bioavailability can be generally documented by a systemic exposure profile obtained by measuring drug or metabolite concentration in the systemic circulation overtime.

(3) Bioequivalence study is conducted to ensure therapeutic equivalence between two pharmaceutically equivalent test product and a reference product.

(4) Bioavailability or Bioequivalence study is conducted to ensure therapeutic equivalence between an approved new drug formulation and reference product for subsequent applicant.

(5) Bioavailability or Bioequivalence study is also conducted to ensure therapeutic equivalence at any phase of clinical trial of a new chemical entity for establishing bioequivalence between two products of the chemical entity, which is important for certain pharmaceutical formulation or manufacturing changes occurring during the drug development stages.

(6) For drugs approved elsewhere in the world and absorbed systemically, bioequivalence with the reference formulation should be carried out wherever applicable. These studies should be conducted under the labelled conditions of administration. Data on the extent of systemic absorption may be required for formulations other than those designed for systemic absorption.

(7) Evaluation of the effect of food on absorption following oral administration should be carried out. Data from dissolution studies should also be submitted for all solid oral dosage forms.

(8) Dissolution and bioavailability data submitted with the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulations sought to be marketed and those used for clinical trials during clinical development of the product.

(9) All bioavailability and bioequivalence studies should be conducted according to the Guidelines for Bioavailability and Bioequivalence studies issued by Central Drugs Standard Control Organisation, Ministry of Health and Family Welfare.

(10) Bioavailability and bioequivalence studies of a new drug or investigational new drug shall be conducted in a bioavailability and bioequivalence study centre registered under rule 47 after obtaining permission from the Central Licencing Authority.

2. Bioavailability and bioequivalence study centre:

2.1 The Bioavailability and bioequivalence study centre shall have following facilities for conducting bioavailability and bioequivalence study of any new drug or investigational new drug:

(2.1.1) Legal Identity: The organization, conducting the bioavailability or bioequivalence studies, or the parent organization to which it belongs, must be a legally constituted body with appropriate statutory registrations.

(2.1.2) Impartiality, confidentiality, independence and integrity: The organization shall:

(a) have managerial staff with the authority and the resources needed to discharge their duties.

(b) have arrangements to ensure that its personnel are free from any commercial, financial and other pressures which might adversely affect the quality of their work.

(c) be organised in such a way that confidence in its independence of judgment and integrity is maintained at all times.

(d) have documented policies and procedures, where relevant, to ensure the protection of its sponsors' confidential information and proprietary rights.

(e) not engage in any activity that may jeopardize the trust in its independence of judgment and integrity

(f) have documented policies and procedures for protection of rights, safety and well -being of study subject in consistent with the Provisions of the Drugs and Cosmetics Act and these Rules and Good Clinical Practices Guidelines

(g) have documented policies and procedures for scientific integrity including procedures dealing with and reporting possible scientific misconduct.

(2.1.3) Organisation and management: The study centre must include the following:

(a) An Investigator who has the overall responsibility to provide protection for safety of the study subject. The Investigator(s) should possess appropriate medical qualifications and relevant experience for conducting pharmacokinetic studies.

(b) The site should have facilities and identified adequately qualified and trained personnel to perform the following functions:

(i) Clinical Pharmacological Unit (CPU) management

(ii) Analytical laboratory management

(iii) Data handling and interpretation

(iv) Documentation and report preparation

(v) Quality assurance of all operations in the centre

(2.1.4) Documented Standard Operating Procedures: (1) The center shall establish and maintain a quality system appropriate to the type, range and volume of its activities. All operations at the site must be conducted as per the authorised and documented standard operating procedures.

(2) These documented procedures should be available to the respective personnel for ready reference. The procedures covered must include those that ensure compliance with all aspects of provision of the Act and these rules, good clinical practices guidelines and good laboratory practice guidelines.

(3) A partial list of procedures for which documented standard operating procedures should be available includes:

(a) maintenance of working standards (pure substances) and respective documentation;

(b) withdrawal, storage and handling of biological samples;

(c) maintenance, calibration and validation of instruments;

(d) managing medical as well as non-medical emergency situations;

(e) handling of biological fluids;

(f) managing laboratory hazards;

(g) disposal procedures for clinical samples and laboratory wastes;

(h) documentation of clinical pharmacology unit observations, volunteer data and analytical data;

(i) obtaining informed consent from volunteers;

(j) volunteer screening and recruitment and management of ineligible volunteers;

(k) volunteer recycling (using the same volunteer for more than one study;

(l) randomization code management;

(m) study subject management at the site (including check-in and check-out procedures);

(n) recording and reporting protocol deviations;

(o) recording, reporting and managing scientific misconduct;

(p) monitoring and quality assurance.

(4) Wherever possible, disposable (sterile, wherever applicable) medical devices must be used for making subject interventions.

(5) If services of a laboratory or a facility other than those available at the site (whether with in India or outside the country) are to be availed – its or their names, address and specific services to be used should be documented.

2.1.5) Clinical Pharmacological Unit

(1) It must have adequate space and facilities to house at least 16 volunteers. Adequate area must be provided for dining and recreation of volunteers, separate from their sleeping area.

(2) Additional space and facilities should also be provided for the following:

(a) Office and administrative functions.

(b) Sample collection and storage.

(c) Control sample storage.

(d) Wet chemical laboratory.

(e) Instrumental Laboratory.

(f) Library.

(g) Documentation archival room.

(h) Facility for washing, cleaning and Toilets.

(i) Microbiological laboratory (Optional).

(j) Radio Immuno-Assay room (optional).

3. Maintenance of Records: All records of in *vivo* or in *vitro* tests conducted on any batch of a new drug product to assure that the product meets a bioequivalence requirement shall be maintained by the Sponsor for at least five years after the completion of any study or for at least two years after the expiration date of the batch of the new drug product whichever is later.

4. Retention of Samples: (1) All samples of test and reference drug products used in bioavailability or bioequivalence study should be retained by the organisation carrying out the bioavailability or bioequivalence study for a period of five years after the conduct of the study or one year after the expiry of the drug, whichever is later.

(2) The study sponsor or drug manufacturer should provide to the testing facility batches of the test and reference drug products in such a manner that the reserve samples can be selected randomly.

(3) This is to ensure that the samples are in fact representative of the batches provided by the study sponsor or drug manufacturer and that they are retained in their original containers. Each reserve sample should consist of a quantity sufficient to carry out twice all the in-vitro and in- vivo tests required during bioavailability or bioequivalence study.

(4) The reserve sample should be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorised personnel.

TABLE 1

DOCUMENT REQUIRED FOR REGISTRATION OF BIOAVAILABILITY AND BIOEQUIVALENCE CENTRE

(1) Name and address of the organization to be registered along with its telephone no., fax no. and email address.

(2) Document regarding legal identity of the centre

(3) Name and address of the proprietors or partners or directors.

(4) An organogram of the centre including brief Curriculum Vitae of Key personnel (Refer para 2.1.3 of this Schedule)

(5) Documents to ensure Impartiality, confidentiality, independence and integrity of the centre**.** Refer para 2.1.2 of this Schedule.

(6) List of equipment in the firm.

(7) List of staff in firm.

(8) List of Standard Operating Procedures for various activities (refer 2.1.4 of this Schedule).

(9) Layout of facility.

(10) Details of Ethics Committee including its registration number.

(11) Facilities for maintenance of records.

(12) Details of Retention of samples.

(13) All major tie ups for ancillary services like ambulance, hospital etc.

TABLE 2
DATA AND INFORMATION REQUIRED FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF A NEW DRUG OR INVESTIGATIONAL NEW DRUG

1. Introduction: A brief description of the drug and the therapeutic class to which it belongs.

2. Chemical and pharmaceutical information, Animal pharmacological and toxicological data, Clinical trial data - As per Second Schedule.

3. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects or patients demonstrating safety and tolerability of the molecule.

4. Regulatory status in other countries: Countries where the drug is,-

(a) Marketed.

(b) Approved.

(c) Approved as Investigational New Drug.

(d) Withdrawn, if any, with reasons.

Restrictions on use, if any, in countries where marketed or approved

Free sale certificate or certificate of analysis, as appropriate.

5. Prescribing information of the new drug in case the drug is approved for marketing in the country or other country.

6. Undertaking by the Investigator in original duly signed on a company letterhead as per Table 4 of the Third Schedule.

7. Copy of registration certificate issued by Central Licencing Authority.

8. Sponsor's Authorisation letter duly signed by the Authorised Signatory on company letterhead.

9. The study protocols, informed consent form or patient information sheet along with audio-visual recording system as per requirements of Second Schedule

10. Copy of approval of protocol from the Ethics committee, if available. Copy of registration of the Ethics Committee under rule 8 from the Central Licencing Authority.

11. The study synopsis.

12. Undertaking letter from the sponsor stating that complete medical management in accordance with rule 40 and an undertaking letter from the sponsor stating that compensation in case of study relate injury or death shall be provided in accordance with rule 39.

13. Certificate of Analysis (COA) of representative batches (both Test and Reference formulations) to be used in the BE study along with dissolution profile in case Oral Solid dosage forms.

14. For multiple dose BE study adequate supporting safety data and Pharamcokinetics or Pharmacodynamics should be submitted covering the duration of period for which the study has to be conducted. For all injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days. If regulatory guidance is available provide a copy of the same.

15. For conducting Bio-Equivalence studies with reference to Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Healthy Human subjects a Scientific justification with special emphasis on safety of subjects with a proper risk mitigation strategy should be submitted. If regulatory guidance is available provide a copy of the same.

16. For conducting Bio-Equivalence studies with reference to cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Patients a scientific justification with special emphasis on Safety with a proper Risk Mitigation Strategy should be submitted.

Note 1: All items may not be applicable to all drugs. For explanation, refer text of this First Schedule, Second Schedule and Third Schedule.

TABLE 3

DATA AND INFORMATION REQUIRED FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF A NEW DRUG ALREADY APPROVED IN THECOUNTRY

1. Introduction: A brief description of the drug and the therapeutic class to which it belongs.
2. Chemical and pharmaceutical information **-** As per Table 2 of Second Schedule
3. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects or patients demonstrating safety and tolerability of the molecule.
4. Prescribing information
5. Undertaking by the Investigator in original duly signed on a company letterhead as per Table 4 of Third Schedule.
6. Copy of registration certificate issued by Central Licencing Authority.
7. Sponsor's authorisation letter duly signed by the Authorised Signatory on company letterhead.
8. The study protocols, Informed Consent Form or Patient Information Sheet along with audio-visual recording system as per requirements of Second Schedule.
9. Copy of approval of protocol from the Ethics Committee, if available.
10. Copy of registration of the Ethics Committee under rule 8 from the Central Licencing Authority.
11. The study synopsis.
12. Undertaking letter from the sponsor stating that complete medical management in accordance with rule 40 and an undertaking letter from the sponsor stating that compensation in case of study relate injury or death shall be provided in accordance with rule 39.
13. Certificate of Analysis (COA) of representative batches (both Test and Reference formulations) to be used in the Bio-Equivalence study along with dissolution profile in case Oral Solid dosage forms.
14. For multiple dose BE study adequate supporting safety data and Pharmacokinetics or Pharmacodynamics should be submitted covering the duration of period for which the study has to be conducted.
15. For all Injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days. If regulatory guidance is available provide a copy of the same.
16. For conducting Bio-Equivalence studies with reference to Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in healthy human subjects a Scientific justification with special emphasis on Safety of subjects with a proper risk mitigation strategy should be submitted. If regulatory guidance is available provide a copy of the same.
17. For conducting Bio-Equivalence studies with reference to cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Patients a scientific justification with special emphasis on Safety with a proper risk mitigation strategy should be submitted.

FIFTH SCHEDULE

POST MARKET ASSESSMENT

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(*See rules 77 and 82*)

1. Post marketing assessment of new drug. - (1) When a new drug is approved for marketing, assessment of safety and efficacy of the drug are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials. Often, high risk patients and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.

(2) In actual clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed. Therefore, subsequent to approval of a new drug, the drug shall be closely monitored and post marketing assessment of its benefit-risk profile shall be carried out once it is marketed.

(3) A person intending to import or manufacture any new drug for sale or distribution shall have a pharmacovigilance system in place for collecting, processing and forwarding the adverse drug reaction report to the Central Licencing Authority emerging from the use of the drug imported or manufactured or marketed by the applicant in the country.

(4) The pharmacovigilance system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports.

(5) Post marketing assessment of new drug may be carried out, in different ways as under:-

(A) Phase IV (Post marketing) trial.- Phase IV (Post marketing) trial include additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trial will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population.

In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines.

In such study, the study drug may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the drug free of cost, to the satisfaction of the Central Licencing Authority and the ethics committee.

(B) Post marketing surveillance study or observational or non-interventional study for active surveillance.- Such studies are conducted with a new drug under approved conditions of its use under a protocol approved by Central Licencing Authority with scientific objective. Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package insert.

In such studies the study drugs are the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable in such cases as drugs are already approved for marketing.

(C) Post marketing surveillance through periodic safety update reports.- As part of post marketing surveillance of new drug the applicant shall furnish periodic safety update reports (PSURs) in accordance with the procedures as follows;

(i) The applicant shall furnish periodic safety update reports (PSURs) in order to-

(a) report all relevant new information from appropriate sources;

(b) relate the data to patient exposure;

(c) summarise the market authorisation status in different countries and any significant variations related to safety; and

(d) indicate whether changes shall be made to product information in order to optimise the use of product.

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one periodic safety update reports. Within the single periodic safety update reports separate presentations of data for different dosage forms, indications or separate population need to be given.

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The periodic safety update reports shall be submitted every six months for the first two years after

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approval of the drug is granted to the applicant. For subsequent two years - the periodic safety update reports need to be submitted annually. Central Licencing Authority may extend the total duration of submission of periodic safety update reports if it is considered necessary in the interest of public health. Periodic safety update reports due for a period must be submitted within thirty calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licencing authority within fifteen days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(iv) New studies specifically planned or conducted to examine a safety issue should be described in the periodic safety update reports.

(v) A PSUR should be structured as follows:

(a) Title Page: The title page of periodic safety update reports should capture the name of the drug; reporting interval; permitted indication of such drug; date of permission of the drug; date of marketing of drug; licencee name and address.

(b) Introduction: This section of periodic safety update reports should capture the reporting interval; drugs intended use, mode of action, therapeutic class, dose, route of administration, formulation and a brief description of the approved indication and population.

(c) Current worldwide marketing authorisation status: This section of periodic safety update reports should capture the brief narrative over view including details of countries where the drug is currently approved along with date of first approval, date of marketing and if product was withdrawn in any of the countries with reasons thereof.

(d) Actions taken in reporting interval for safety reasons: This section of periodic safety update reports should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the licence holder, sponsor of a clinical trial, regulatory authorities, data monitoring committees, or ethics committees.

(e) Changes to reference safety information: This section of periodic safety update reports should capture any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, adverse events, and important findings from ongoing and completed clinical trials and significant non-clinical findings.

(f) Estimated patient exposure: This section of periodic safety update reports should provide the estimates of the size and nature of the population exposed to the drug. Brief descriptions of the methods used to estimate the subject or patient exposure should be provided,-

(i) Cumulative and interval subject exposure in clinical trial.

(ii) Cumulative and interval patient exposure from Marketing Experience from India.

(iii) Cumulative and interval patient exposure from Marketing Experience from rest of the world.

(g) Presentation of individual case histories: This section of periodic safety update reports should include the individual case information available to a licence holder and provide brief case narrative, medical history indication treated with suspect drug, causality assessment. Provide following information:

(i) Reference prescribing information

(ii) Individual cases received from India

(iii) Individual cases received from rest of the world

(iv) Cumulative and interval summary tabulations of serious adverse events from clinical investigations.

(v) Cumulative and interval summary tabulations from post-marketing data sources

(h) Studies: This section of periodic safety update reports should capture the brief summary of clinically important emerging efficacy or effectiveness and safety findings obtained from the licence holder, sponsored clinical trials and published safety studies that became available during the reporting interval of the report which has potential impact on product safety information.

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(i) Summaries of significant safety findings from clinical trials during the reporting period;

(ii) Findings from non-interventional Studies;

(iii) Findings from non-Clinical Studies;

(iv) Findings from literature.

(i) Other information: This section of periodic safety update reports should include the details about signals and Risk Management Plan in place by licence holder (if any).

(a) Signal and risk evaluation: In this section licence holder will provide the details of signal and risk identified during the reporting period and evaluation of signals identified during the reporting period.

(b) Risk management plan: In this section licence holder will provide the brief details of safety concern and necessary action taken by him to mitigate these safety concerns.

(j) Overall Safety Evaluation: This section of periodic safety update reports should capture the overall safety evaluation of the drug based upon its risk benefit evaluation for approved indication.

(i) Summary of safety concerns

(ii) Benefit evaluation

(iii) Benefit risk analysis evaluation

(k) Conclusion: This section of periodic safety update reports should provide the details on the safety profile of drug and necessary action taken by the licence holder in this regards.

(l) Appendix: The appendix includes the copy of marketing authorisation in India, copy of prescribing information, line listings with narrative of Individual Case Safety Reports (ICSR).

SIXTH SCHEDULE

(S*ee rules 21, 22, 33, 34, 45, 47, 52, 53, 60, 67, 68, 75, 76, 80, 81, 86, 91, 97 and 98*)

FEE PAYABLE FOR LICENCE, PERMISSION AND REGISTRATION CERTIFICATE

Serial Number	Rule	Subject	In rupees Indian National Rupee (INR) except where specified in dollars ($)
01	21	Application for permission to conduct clinical trial	
		(i) Phase I	3,00,000
		(ii) Phase II	2,00,000
		(iii)Phase III	2,00,000
		(iv) Phase IV	2,00,000
02	22	Reconsideration of application for permission to conduct clinical trial	50,000
03	33	Application for permission toconduct bioavailability or bioequivalence study	2,00,000
04	34	Reconsideration of application of permission to conduct bioavailability or bioequivalence study	50,000

05	45	Application for registrationof bioavailability and bioequivalence study centre	5,00,000
07	47	Reconsideration of application for Registration of bioavailability and bio-equivalence study centre	1,00,000
08	52	Application for permission to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study	5000 per product
09	53	Reconsideration of application to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study	2000 per product
10	59	Application for permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study	5000 per product
11	60	Reconsideration of permission to Manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study	2000
12	67	Application for import of new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis	5000 per product
13	68	Reconsideration of application for Import of new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis	1000
14	75	Application for permission to import new drug (Finished Formulation) for marketing	5,00,000
15		Application for permission to import new Drug (Finished Formulation) already approved in the country for marketing	2,00,000
16		Application for permission to import new drug (Active Pharmaceutical Ingredient) for marketing	5,00,000

17		Application for permission to import new drug (Active Pharmaceutical Ingredient) already approved in the country for marketing	2,00,000
18		Application for permission to import approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for marketing	3,00,000
19		Application for permission to import fixed dose combination having one or more of the ingredients as unapproved new molecules for marketing	5,00,000
20		Application for permission to import fixed Dose combination having approved ingredients for marketing	4,00,000
21		Application for permission to import fixed dose combination already approved for marketing	2,00,000
22		Application for permission to import fixed dose combination for new claims, new indication or new dosage form or new route of administration or new strength for marketing	3,00,000
23	76	Reconsideration of application for permission to import new drug for marketing	50,000

24	80	Application for permission to manufacture new drug (Finished Formulation or Active Pharmaceutical Ingredient) for sale or distribution	5,00,000
25		Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) already approved in the country for sale or distribution	2,00,000
26		Application for permission to manufacture new drug (Finished Formulation) for sale or distribution	5,00,000
27		Application for permission to manufacture new drug (Finished Formulation) already approved in the country for sale or distribution	2,00,000
28		Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) for sale or distribution	5,00,000

29		Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) already approved in the country for sale or distribution	2,00,000
30		Application for permission to manufacture approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for sale or distribution	3,00,000
31		Application for permission to manufacture fixed dose combination having one or more of the ingredients as unapproved new molecules for sale or distribution	5,00,000
32	80	Application for permission to manufacture fixed dose combination having approved ingredients for sale or distribution	3,00,000
33		Application for permission to manufacture fixed dose combination already approved for sale or distribution	2,00,000
34		Application for permission to manufacture fixed dose combination for new claims, new indication or new dosage form or new route of administration or new strength for sale or distribution	3,00,000

35	80	Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) or to manufacture finished formulation	5,00,000
36		Application for permission to import or to manufacture phyto-pharmaceutical drugs	2,00,000
		Reconsideration of application for	
37	81	permission to manufacture new drug for sale or distribution	50,000
		Application for Import of unapproved new	
38	86	drug by Government hospital and medical institution	10,000
		Application for permission to manufacture unapproved new drug but under clinical	
39	91	trial, for treatment of patient of life threatening disease	5,000
40	98	Pre-submission meeting	5,00,000
41	99	Post-submission meeting	50000
42	-	Any other application which is not specified above	50000

Note 1: No fee shall be chargeable in respect of application for conduct of clinical trial for orphan drugs as defined in clause (x) of rule 2.

Note 2: In case of application received from Micro Small Medium Enterprises (MSME) firms for conduct of clinical trial, approval of new drug and pre and post submission meeting, the fee payable shall be half of the fee specified above.

SEVENTH SCHEDULE

(*See rules 39, 40, and 42*)

FORMULAE TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED INJURY OR DEATH

1. Formula in case of clinical trial related death:

Compensation = (B x F x R) / 99.37

Where,

B = Base amount (i.e. 8 lacs)

F = Factor depending on the age of the trial subject as per **Annexure 1** (based on Workmen Compensation Act)

R = Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the trial subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

(1) 0.5 terminally ill patient (expected survival not more than (NMT) 6 months)

(2) 1.0 Patient with high risk (expected survival between 6 to 24months)

(3) 2.0 Patient with moderate risk

(4) 3.0 Patient with mild risk

(5) 4.0 Healthy Volunteers or trial subject of no risk.

However, in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of Rs. 2 lacs should be given.

2. Formula in case of clinical trial related injury (other than death): For calculation of quantum of compensation related to injury (other than death), the compensation shall be linked to the criteria considered for calculation of compensation in cases of death of the trial subject as referred to in section of this Schedule. The quantum of compensation in case of Clinical Trial related SAE should not exceed the quantum of compensation which would have been due for payment in Case of death of the trial subject since the loss of life is the maximum injury possible.As per the definition of SAE, the following sequelae other than death are possible in a clinical trial subject, in which the trial subject shall be entitled for compensation in case the SAE is related to clinical trial.

(i) A permanent disability: In case of SAE causing permanent disability to the trial subject, the quantum of compensation in case of 100% disability shall be 90% of the compensation which would have been due for payment to the nominee (s) in case of death of the trial subject.

The quantum for less than 100% disability will be proportional to the actual percentage disability the trial subject has suffered.

Accordingly, following formula shall be applicable for determination of compensation:

Compensation = (C x D x 90) / (100 x 100)

Where:

D = Percentage disability the trial subject has suffered.

C = Quantum of Compensation which would have been due for payment to the trial subject's nominees)

in case of death of the trial subject.

(ii) Congenital anomaly or birth defect: The congenital anomaly or birth defect in a baby may occur due to participation of anyone or both the parent in clinical trial. Following situations may arise due to congenital anomaly or birth defect.

(a) Still birth;

(b) Early death due to anomaly;

(c) No death but deformity which can be fully corrected through appropriate intervention;

(d) Permanent disability (mental or physical).

The compensation in such cases would be a lump sum amount such that if that amount is kept by way of fixed deposit or alike, it shall bring a monthly interest amount which is approximately equivalent to half of minimum wage of the

unskilled worker (in Delhi). The quantum of compensation in such cases of SAE shall be half of the base amount as per formula for determining the compensation for SAE resulting into death.

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In case of birth defect leading to sub-clause (c) and (d) of this clause to any child, the medical management as long as required shall be provided by the Sponsor or his representative which will be over and above the financial compensation.

(iii) Chronic life-threatening disease; and

(iv) Reversible SAE in case it is resolved.

In case of clinical trial related SAE causing life-threatening disease and reversible SAE in case it is resolved, the quantum of compensation would be linked to the number of days of hospitalisation of the trial subject. The compensation per day of hospitalization shall be equal to the wage loss. The wage loss per day shall be calculated based upon the minimum wage of the unskilled worker (in Delhi).

Since, in case of hospitalisation of any patient not only the patient loses his/her wage, there will be direct or indirect losses of various kind including inconvenience, wage loss of attendant, etc. The compensation per day of hospitalisation in such case shall be double the minimum wage.

Accordingly, following formula shall be applicable for determination of compensation:

Compensation = 2 X W X N.

Where,

W = Minimum wage per day of the unskilled worker (in Delhi)

N = Number of days of hospitalization

Annexure 1

Factor (F) for calculating the amount of compensation

Age	Factor
Not more than...	
16	228.54
17	227.49
18	226.38
19	225.22
20	224.00
21	222.71
22	221.37
23	219.95
24	218.47
25	216.91
26	215.28
27	213.57
28	211.79
29	209.92
30	207.98
31	205.95
32	203.85
33	201.66
34	199.40
35	197.06
36	194.64
37	192.14
38	189.56
39	186.90
40	184.17
41	181.37
42	178.49
43	175.54
44	172.52
45	169.44
46	166.29
47	163.07

48	159.80
49	156.47
50	153.09
51	149.67
52	146.20
53	142.68
54	139.13
55	135.56
56	131.95
57	128.33
58	124.70
59	121.05
60	117.41
61	113.77
62	110.14
63	106.52
64	102.93
65 or more	99.37

EIGHTH SCHEDULE

FORM CT-01

(*See rules 8, 10 and 17*)

APPLICATION FOR REGISTRATION/RENEWAL OF ETHICS COMMITTEE RELATING TO CLINICAL TRIAL OR BIOAVAILABILITY AND BIOEQUIVALNENCE STUDY OR BIOMEDICAL HEALTH RESEARCH

I/We, ...*(name, designation and full postal address of the applicant)* of ..... (*name and full address with contact details of the ethics committee*) hereby apply for grant of registration of ethics committee.

The details of the application are as under:

1. Name of applicant:
2. Nature and constitution of applicant: (proprietorship, company, society, trust, independent, institutional, other to be specified)
3. (i) Applicant address including telephone number, mobile number, fax number and e-mail id: (ii) Address for correspondence: corporate or registered office or clinical trial site or bioavailability and bioequivalence study centre or biomedical health research
4. Details of accreditation, if any (self-attested copy of certificate to be attached):
5. I have enclosed the documents as specified in the Table 1 of the Third Schedule of the New Drugs and Clinical Trials Rules, 2019.

6. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.

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Place: _____ Digital Signature

Date: _____ (Name and designation)

FORM CT-02

(*See rules 8, 9, 10 and 14)*

GRANT OF REGISTRATION OF ETHICS COMMITTEE RELATING TO CLINICAL TRIAL OR BIOAVAILABILITY AND BIOEQUIVALNENCE STUDY

Registration No._____

The Central Licencing Authority here by registers and permits___(Name and full address with contact details of the ethics committee) to perform duties of ethics committee as specified in the New Drugs and Clinical Trials Rules, 2019.

2. The ethics committee shall observe the conditions of registration specified in Chapter III of the New Drugs and Clinical Trials Rules, 2019 and the Drugs and Cosmetics Act, 1940.

Place: …… Central Licencing Authority

Date: ..... Stamp

FORM CT-03

(*See rules 17 and 18)*

GRANT OF REGISTRATION OF ETHICS COMMITTEE RELATING TO BIOMEDICAL HEALTH RESEARCH

Registration No._____

The designated authority is hereby register and permit_____
(Name and full address with contact details of the ethics committee) to perform duties of ethics committee as specified in the Regulation of New Drugs and Clinical Trials Rules, 2019.

2. The ethics committee shall observe the conditions of registration specified in Chapter IV of the New Drugs and Clinical Trials Rules, 2019 and the Drugs and Cosmetics Act, 1940.

Place: …… Central Licencing Authority

Date: ..... Stamp

FORM CT-04

(*See rule 21*)

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APPLICATION FOR GRANT OF PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to conduct clinical trial on new drug or investigational new drug.

The details of the application are as under:

1.Name of Applicant:	
2. Nature and constitution: proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified.	
3. (i) Sponsor address, telephone number, mobile number, fax number and e-mail id: (ii) Clinical trials site address, telephone number, mobile number, fax number and e-mail id: (iii) Name and address of person responsible for payment of compensation, if any: (iv) Address for correspondence: [corporate or registered office or clinical trial site]	
4. Details of new drugs or investigational new drugs and clinical investigation site [As per Annexure].	
5. Phase of the Clinical Trial	
6. Clinical trial protocol number with date:	
7. Fee paid on _____ Rs. _____ Receipt or Challan or transaction ID_____.	
8. I have enclosed the documents as specified in the Second Schedule of the New Drugs and Clinical Trials Rules, 2019.	
9. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.	

Place:……. Digital Signature

Date:……..... (Name and designation)

Annexure:

Details of new drugs or investigational new drugs:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	

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Composition:	
Indications:	

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of investigator:	

FORM CT-4A

(*See rule 23*)

INFORMATION TO INITIATE CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG AS PART OF DISCOVERY, RESEARCH AND MANUFACTURE IN INDIA

I/We, ...*(name and full postal address of the applicant)* of ..... hereby inform to initiate the conduct clinical trial on new drug or investigational new drug.

The details of the application areas under:

1.Name of Applicant:	
2. Nature and constitution: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3. (i) Sponsor address, telephone number, mobile number, fax number and e-mail id: (ii) Clinical trials site address, telephone number, mobile number, fax number and e-mail id: (iii) Name and address of person responsible for payment of compensation, if any: (iv) Address for correspondence: [corporate or registered office or clinical trial site]	
4. Details of new drugs or investigational new drugs and clinical investigation site [As per Annexure].	
5. Phase of the Clinical Trial	
6. Clinical trial protocol number with date:	
8. I hereby declared that I have already submitted the application under rule 21 of these rules and granted automatic approval under rule 23(2) and enclosed the documents as specified in the Second Schedule of the New Drugs and Clinical Trials rules, 2019.	
9. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.	

Place:……. Digital Signature

Date:……..... (Name and designation)

Annexure:

Details of new drugs or investigational new drugs:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of investigator:	

FORM CT-05

(See rule 33)

APPLICATION FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to conduct bioavailability or bioequivalence study (*strike off whichever is not applicable*) of new drug or investigational new drug, the details of which are as under:

1.Name of applicant:	
2. Nature and constitution: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3. (i) Sponsor address, telephone number, mobile number, fax number and e-mail id: (ii) Study address, telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence: [corporate or registered office or bioavailability or bioequivalence study centre]	

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4. Details of new drug or investigational new drug and study centre [As per Annexure].
5. Study protocol number with date:
6. Fee paid on _____ Rs. _____ Receipt or challan or transaction ID_____.
7. I have enclosed the documents as specified in the Fourth Schedule of the New Drugs and Clinical Trials Rules, 2019.
8. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.

Place:……. Digital Signature

Date:……..... (Name and designation)

Annexure:

Details of new drug or investigational new drugs:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of study centre:

Names and address of study centre	
Ethics committee details:	

FORM CT-06

(See rules 22, 25, 26, 29 and 30)

PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licencing Authority hereby permits_____

(Name and full address with contact details of the applicant) to conduct clinical trial of the new drug or investigational new drug as per protocol number _____in the below mentioned clinical trial sites. dated

2. Details of new drug or investigational new drug and clinical trial site [As per Annexure].

3. This permission is subject to the conditions prescribed in part A of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

Place: ……. Central Licencing Authority

Date: ..... Stamp

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of principal investigator:	

FORM CT-07

(See Rules 34, 35, 36, 37 and 38)

PERMISSION TO CONDUCT BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licencing Authority hereby permits_____
(Name and full address with contact details of the applicant) to conduct bioavailability or bioequivalence study (*strike off whichever is not applicable*) of the new drug or investigational new drug as per protocol number_____dated___in the below mentioned study centre.

2. Details of new drug or investigational new drug and study centre [As per Annexure].

3. This permission is subject to the conditions prescribed in part B of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

Place: …… Central Licencing Authority

Date: ..... Stamp

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of study centre:

Names and address of study centre:	
Ethics committee details:	
Name of principal investigator:	

FORM CT-08

(*See rule45*)

APPLICATION FOR REGISTRATION/RENEWAL OF BIOAVAILABILITY OR BIOEQUIVALENCE STUDY CENTRE

I/We, ...*(name, designation and full postal address of the applicant)* of ..... hereby apply for grant of registration of bioavailability or bioequivalence study centre. The details of the application are as under:

1.Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, company, society, trust, independent, institutional, other to be specified)	
3. (i) Applicant address including telephone number, mobile number, fax number and e-mail id: (ii) Address for correspondence: [corporate or registered office or bioavailability or bioequivalence study centre]	
4. Details of accreditation, if any (self-attested copy of certificate to be attached):	
5. Fee paid on _____ Rs. _____ Receipt or challan or transaction ID_____.	
6. I have enclosed the documents as specified in the Table 1 of Fourth Schedule of the New Drugs and Clinical Trials Rules, 2019.	
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 the New Drugs and Clinical Trials Rules, 2019.	

Place: ……..

Date: ……

Digital Signature

(Name and designation)

FORM CT-09

(*See rules 47, 48, 49, 50and 51*)

GRANT OF REGISTRATION OF BIOAVAILABILITY OR BIOEQUIVALENCE STUDY CENTRE

Registration No._____

The Central Licencing Authority hereby register_____
(Name and full address with contact details of the applicant) for conduct of bioavailability and bioequivalence studies of new drugs and investigational new drugs as specified in the New Drugs and Clinical Trials Rules, 2019.

2.This registration is subject to the conditions prescribed in Chapter VII of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

Place: …….
Date: .....

Central Licencing Authority
Stamp

FORM CT-10

(*See rule 52)*

APPLICATION FOR GRANT OF PERMISSION

TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

I/We, ...

(name and full postal address of the applicant) of ..... hereby apply for grant of permission to manufacture new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or Registered office address, telephone number, mobile number, fax number and e-mail id: (ii) Applicant's address, telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of new drugs and investigational new drugs to be manufactured [As per Annexure].	
5. Particulars of Manufacturer, Manufacturing sites [As per Annexure].	
6. Fee paid on _____Rs_____receipt or challan or transaction ID___.	

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7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and the Chapter VIII of New Drugs and Clinical Trials Rules, 2019. (ii) The new drug to be manufactured from M/s..... shall be used exclusively for the purpose of clinical trial and no part of it shall be diverted to the domestic market.	
Place: ……. Date:	Digital Signature (Name and designation)

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of manufacturer and manufacturing site:

Name and address of Active Pharmaceutical Ingredient and formulation manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	
Name and address of manufacturing sites of Active Pharmaceutical Ingredient and formulation (full address with telephone, fax and e-mail address of the manufacturing site).	

FORM CT-11

(*See rules 53, 54, 55, 56, 57 and 58)*

PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL, BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Licence Number _____

The Central Licencing Authority hereby grant permission _____ (Name and full postal address with contact details of the applicant) to manufacture the new drug or investigational new drug for conduct of clinical trial or bioavailability or bioequivalence study as per protocol number_____dated_____in the below mentioned clinical trial sites or bioavailability and bioequivalence study centre [As per Annexure] or for examination, test and analysis.

Serial Number	Name of the new drug or investigational new drug to be manufactured.	Class of new drug or investigational new drug.	Quantity to be manufactured.

2. This licence is subject to the conditions specified in the Chapter VIII of New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act, 1940.

3. This licence shall, unless previously suspended or revoked, be in force for a period of three years from the date of its issuance.

4. Details of manufacturer and manufacturing site under this licence.

Serial Number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

Place: …….

Date: .....

Central Licencing Authority

Stamp

Annexure:

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of investigator:	

FORM CT-12

(*See rule 59)*

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE FORMULATION OF UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to manufacture formulations of unapproved active pharmaceutical ingredient for test or analysis or clinical trial or bioavailability or bioequivalence study.

The details of the application are as under:

1. Name of formulation manufacturer:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address telephone number, mobile number, fax number and e-mail id: (ii) Formulation manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	

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4. Details of unapproved Active pharmaceutical ingredient and its formulation [As per Annexure].
5. Details of Manufacturer, Manufacturing sites of formulation [As per Annexure].
6.Fee paid on _____ Rs__ receipt or challan or transaction ID.
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter VIII of the New Drugs and Clinical Trials Rules, 2019. (ii) The formulation of the unapproved active pharmaceutical ingredient to be manufactured shall be used for the mentioned purpose only and no part of it shall be sold in the market.

Place: Digital Signature

Date: (Name and designation)

Annexure:

Details of Active pharmaceutical ingredient and its formulation:

Name of the unapproved active pharmaceutical ingredient (API)	Quantity	Name of the formulation/test Batches to be developed for test/analysis or clinical trial	Quantity

Name of the formulation to be manufactured	
Quantity	
Composition	
Indication	

Details of manufacturer and manufacturing site of formulation:

Serial number	Name and address of manufacturer of formulation (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of formulation (full address with telephone, fax and e-mail address of the manufacturing site)

Details of manufacturer and manufacturing site of Active pharmaceutical ingredient:

Serial number	Name and address of manufacturer of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturing site)

FORM CT-13

(*See rule 59 and 60)*

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APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR DEVELOPMENT OF FORMULATION FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study.

The details of the application are as under:

1. Name of manufacture:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address telephone number, mobile number, fax number and e-mail id: (ii) Formulation manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of unapproved active pharmaceutical ingredient to be manufactured [As per Annexure].	
5. Details of formulation to be manufactured [As per Annexure].	
6. Fee paid on_____Rs_____ receipt or challan or transaction ID_____.	
(i) I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter VIII of the New Drugs and Clinical Trials Rules, 2019. (ii) The unapproved active pharmaceutical ingredient to be manufactured shall be supplied to M/s ……only and no part of it shall be sold in the market.	

Place: Digital Signature

Date: (Name and designation)

Annexure:

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Details of Active pharmaceutical ingredient and its formulation:

Name of the unapproved active pharmaceutical ingredient (API) to be obtained	Quantity	Name of the formulation or test batches to be developed for test/analysis or clinical trial	Quantity

Details of manufacturer and manufacturing site of formulation:

Serial number	Name and address of manufacturer of formulation (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of formulation (full address with telephone, fax and e-mail address of the manufacturing site)

Details of manufacturer and manufacturing site of Active pharmaceutical ingredient:

Serial number	Name and address of manufacturer of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturing site)

FORM CT-14

(*See rules 60, 61, 62, 63and64*)

PERMISSION TO MANUFACTURE FORMULATION OF UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

Licence Number:_____

The Central Licencing Authority hereby grant permission to _____
(Name and full postal address with contact details of the formulation manufacturer) to manufacture the formulation of the unapproved active pharmaceutical ingredient specified below for test or analysis or for conduct of clinical trials bioavailability or bioequivalence study.

Name of the formulation or test batches to be developed for test or analysis or clinical trial	Quantity

2. Details of manufacturer, manufacturing site of formulation [As per Annexure].

Serial number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

3. This licence is subject to the conditions prescribed under Chapter VII of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

4. Details of manufacturer and manufacturing site of active pharmaceutical ingredient to be supplied.

Serial number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

5. This licence shall, unless previously suspended or revoked, be in force fora period of ..... from the date of its issuance.

Place:…… Central Licencing Authority

Date: ..... Stamp

FORM CT-15

(*See rules 60, 61, 62, 63 and 64*)

PERMISSION TO MANUFACTURE UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR THE DEVELOPEMNT OF FORMULATION FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

Licence Number:_____

The Central Licencing Authority hereby grant permission to_____
(Name and full address of the active ingredient manufacturer) to manufacture the unapproved active pharmaceutical ingredient specified below to manufacture its formulation for test or analysis or for conduct of clinical trials or bioavailability or bioequivalence study.

Name of the unapproved active pharmaceutical ingredient (API) to be manufactured	Quantity

2. Details of Manufacturer, Manufacturing site of active pharmaceutical ingredient.

Serial number	Name and address of manufacturer (full address with telephone, fax and e- mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

3. Details of Manufacturer, Manufacturing site of formulation manufacturer to be supplied.

Serial. number	Name and address of formulator (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of site where the manufactured unapproved active pharmaceutical ingredient to be used (full address with telephone, fax and e-mail address of the manufacturing site)

4. This permission is subject to the conditions specified in Chapter VIII of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act, 1940.

5. This permission shall, unless previously suspended or revoked, be in force for a period of ..... from the date of its issuance.

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Place:…….

Date: .....

Central Licencing Authority

Stamp

Annexure

Details of record of unapproved active pharmaceutical ingredient manufactured:

Serial number	Date of manufacture	Licence number	Name of the unapproved active pharmaceutical ingredient	Quantity manufactured	Manufactured for

Details of reconciliation of unapproved active pharmaceutical ingredient manufactured:

Date	Name of the unapproved active pharmaceutical ingredient	Licence number	Quantity manufactured	Quantity supplied	Quantity remained	Supplied to	Quantity – left over or remain unused or got damaged or expired or found of sub-standard quality	Action taken

*** Write NA where not applicable.**

FORM CT-16

(*See rule 67*)

APPLICATION FOR GRANT OF LICENCE TO IMPORT NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

I/We, ...*(name and address of the applicant)* of M/s ..... hereby apply for grant of licence to import new drug or investigational new drug for clinical trial bioavailability or bioequivalence study or for examination, test and analysis.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	

3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Applicant's address including telephone number, mobile number, fax number and e- mail id: (iii) Address for correspondence:	
4. Details of new drugs to be imported [As per Annexure].	
5. Particulars of overseas Manufacturer, Manufacturing sites [As per Annexure].	
6. Fee paid on _____ Rs_____ receipt or challan or transaction ID.	
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter IX of the New Drugs and Clinical Trials Rules, 2019. (ii) The new drug to be imported from M/s..... shall be used exclusively for the purpose of clinical trial and no part of it shall be diverted to the domestic market.	

Place: Digital Signature

Date: (Name and designation)

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of manufacturer and manufacturing site:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	
Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)	

FORM CT-17

(*See rules 68, 69, 70, 71 and 72*)

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LICENCE TO IMPORT NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR THE PURPOSE OF CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Licence Number:_____

The Central Licencing Authority hereby grants licence to _____(Name and full address with contact details of the applicant) to import new drug or investigational new drug for conduct of clinical trial or bioavailability or bioequivalence study as per protocol number_dated

_____or for examination, test and analysis in the below mentioned clinical trial sites or bioavailability or bioequivalence study centre. [As per Annexure].

Serial number	Name of the new drug or investigational new drug to be imported	Therapeutic class of new drug or investigational new drug	Quantity to be imported

2. This licence is subject to the conditions prescribed in Chapter IX of the New Drugs and Clinical Trials Rules, 2019.

3. This licence shall, unless previously suspended or revoked, be in force for a period of three years from the date of its issuance.

4. Details of overseas manufacturer and manufacturing site under this licence.

Serial number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

5. The licencee shall maintain the record of imported new drug or investigational new drugs [As per Annexure].

Place: ……. Central Licencing Authority

Date: ..... Stamp

Annexure:

Details of clinical trial site or bioavailability or bioequivalence study centre:

Names and address:	
Ethics committee details:	
Name of investigator:	

FORM CT-18

(*See rule 75*)

APPLICATION FOR GRANT OF PERMISSION TO IMPORT NEW DRUG FOR SALE OR FOR DISTRIBUTION

I/We, ... *(name and address of the applicant)* of M/s ..... hereby apply for grant of permission to import new drug for sale.

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1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of new drug to be imported (Active pharmaceutical Ingredient or Finished Formulation) [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Fee paid on _____ Rs_____ receipt or challan or transaction ID_____.	
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter X of the New Drugs and Clinical Trials Rules, 2019.	

Place: Digital Signature

Date: (Name and designation)

Annexure:

Details of new drug:

Name of the new drug:	
Dosage form:	
Composition of the formulation:	
Therapeutic class of the new drug:	
Indications for which proposed to be used:	
Manufacturer of the raw material (active pharmaceutical ingredient):	

Details of manufacturer and manufacturing site of new drug:

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Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

FORM CT-19

(*See rules 76, 77 and 78*)

PERMISSION TO IMPORT NEW ACTIVE PHARMCEUTICAL INGREDIENT FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grants permission to_____
(Name and full postal address of authorised agent with contact details of the organization) to import new active pharmaceutical ingredient manufactured by an overseas manufacturer specified below for sale.

2. Details of overseas manufacturer and its manufacturing site under this licence.

Serial number	Name and address of overseas manufacturer (full name and address with telephone and e-mail address of manufacturer)	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site)

3. This permission is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

4. Details of active pharmaceutical ingredient to be imported.

Name of the active pharmaceutical ingredient to be obtained.	Quantity.

Place: …… Central Licencing Authority

Date: ..... Stamp

FORM CT-20

(*See rules 76, 77 and 78*)

PERMISSION TO IMPORT PHARMACEUTICAL FORMULATIONS OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grant permission to_____
(Name and full postal address of authorised agent with contact details of the organisation) to import pharmaceutical formulation manufactured by an overseas manufacturer specified below for sale.

2. Details of overseas manufacturer and its manufacturing site under this licence.

Serial number	Name and address of overseas manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site)

3. Details of pharmaceutical formulation:

Name of the new drug to be imported:	
Dosage form:	
Composition:	
Indication:	

4. This permission is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

Place: ……. Central Licencing Authority

Date: ..... Stamp

FORM CT-21

(*See rule 80)*

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE NEW DRUG FORMULATION FOR SALE OR FOR DISTRIBUTION

I/We, ... *(name and full postal address of the applicant)* of M/s ..... hereby apply for grant of permission to manufacture new drug for sale or distribution.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (i.e. proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of new drug to be manufactured (Active pharmaceutical Ingredient or Finished Formulation or both) [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Fee paid on _____Rs__ receipt or challan or transaction ID.	

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7. I hereby state and undertake that:

(i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter X of the New Drugs and Clinical Trials Rules, 2019.

Place:……..

Date: ……

Digital Signature

(Name and designation)

Annexure:

Details of new drug:

Name of the new drug:	
Dosage form:	
Composition of the formulation:	
Therapeutic class of the new drug:	
Indications for which proposed to be used:	

Details of manufacturer and manufacturing site of new drug:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

FORM CT-22

(*See rules 81, 82, 83 and 84*)

PERMISSION TO MANUFACTURE NEW ACTIVE PHARMACEUTICAL INGREDIENT FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grant permission to …… (Name and full address with contact details of the manufacturer) to manufacture for sale the new active pharmaceutical ingredient manufactured by manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this permission.

Serial number	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer)	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site)

3. This is subject to the conditions specified in Chapter X of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

4. Details of the new active pharmaceutical ingredient to be manufactured------.

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Place: …….

Date: .....

Central Licencing Authority

Stamp

FORM CT-23

(*See rules 81, 82, 83 and 84*)

PERMISSION TO MANUFACTURE PHARMACEUTICAL FORMULATION OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grant permission to …… (Name and full address of authorised agent with contact details of the manufacturer) to manufacture for sale of pharmaceutical formulation manufactured by an manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this licence.

Serial number	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site).

3. Details of pharmaceutical formulation:

Name of the new drug to be imported:	
Dosage form:	
Composition:	
Indication:	
Shelf life with storage condition:	

4. This is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act,1940.

Place: …….

Date: .....

Central Licencing Authority

Stamp

FORM CT-24

(See rule 86)

APPLICATION FOR LICENCE TO IMPORT OF UNAPPROVED NEW DRUG FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR GOVERNMENT MEDICAL INSTITUTION

I/We, ...

(name and full postal address of the applicant) of M/s ..... hereby apply for grant of licence to import unapproved new drug but under clinical trial for treatment of patients of life threatening disease in a government hospital or medical institution.

The details of the application are as under:

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1. Name of Medical officer:	
2. Nature and constitution of applicant: (Government Hospital or Medical Institution)	
3.(i) Aaddress including telephone number, mobile number, fax number and e-mail id of the Government Hospital or Medical Institution: (ii) Address for correspondence:	
4. Details of unapproved new drug pharmaceutical formulation to be imported [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Details of the patient and disease [As per Annexure].	
7. Fee paid on _____ Rs__ receipt or challan or transaction ID.	
8. A legal undertaking stating that the unapproved new drug to be imported shall be used for the treatment of the patient for the disease mentioned below only and no part of it shall be sold in the market is enclosed herewith.	

Place: …… Digital Signature

Date: ……. (Name and designation)

Annexure:

Details of unapproved new drug to be imported:

Name of the new drug:	
Dosage form:	
Quantity:	
Indications for which proposed to be used:	

Details of manufacturer and manufacturing site:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

Details of patient:

Name of the patient:	
Disease name:	

Certificate

Certified that the unapproved new drug specified above for import is urgently required for the treatment of patients suffering from…….. and that the said drug is not available in India. 172

Place..... Signature

Date..... Medical Superintendent of the Government Hospital or Head of Medical Institution

[Stamp]

FORM CT-25

(See rules 87, 88, 89 and 90)

LICENCE TO IMPORT UNAPPROVED NEW DRUG FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR MEDICAL INSTITUTION

Licence Number:_____

The Central Licencing Authority hereby grant license to_____(Name and full postal address with contact details of the Government Hospital or Government Medical Institution) to import the unapproved new drug specified below for the purpose of treatment of the patient for the disease …… (Name of the disease).

2. This permission is subject to the conditions prescribed in Chapter XI of the New Drugs and Clinical trials Rules,2019 under the Drugs and Cosmetics Act, 1940.

3. This licence shall, unless previously suspended or revoked, be in force for a period of ..... from the date of its issuance.

4. Details of the new drug to be imported

Name of new drug:	
Quantity to be imported:	

Place: ……. Central Licencing Authority

Date: ..... Stamp

Annexure

Details of new drug imported:

Serial number	Date of import.	Licence number	Name of the new drug imported.	Imported through (Port office name).	Consignment number	Quantity imported.

Details of record of patient history:

Licence number	Name of the new drug.	Patient name	Diagnosis detail with date.	Disease name.	Dosage schedule.

Details of reconciliation of new drug to be imported:

Date	Nam e of the new drug.	Licence number.	Initial quantity.	Quantity used.	Quantity remained.	Quantity – left over or remain unused or got damaged or expired or found of sub-standard quality	Action taken.

*Write NA where not applicable.

FORM CT-26

(See rule 91)

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE UNAPPROVED NEW DRUG BUT UNDER CLINICAL TRIAL FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR MEDICAL INSTITUTION

I/We, ... *(name and full postal address of the applicant)* of M/s ..... hereby apply for grant of permission to manufacture unapproved new drug but under clinical trial for treatment of patients of life threatening disease in a government hospital or medical institution.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of unapproved new drug to be manufactured [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Details of the Medical officer and Government Hospital and Medical Institution	
7. Copy of recommendation of the ethics committee and consent from the patient in accordance with Rule 81 of the Regulation of New Drugs and Clinical Trials Rules 2019 are hereby enclosed.	

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8. Fee paid on _____Rs_____ receipt or challan or transaction ID___.
9. A legal undertaking stating that the unapproved new drug to be manufactured shall be used for the treatment of the patient for the disease mentioned below only and no part of it shall be sold in the market is enclosed herewith.

Place:……. Digital Signature

Date: ……. (Name and designation)

Annexure:

Details of unapproved new drug to be manufactured:

Name of the new drug:	
Quantity:	
Indications:	

Details of manufacturer and manufacturing site:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

Details of the government hospital or government medical institution and patient:

Name of the government hospital or government medical institution:	
Address of the government hospital or government medical institution:	
Name and address of the patient:	
Disease name:	

Certificate

Certified that the unapproved new drug but under clinical trial specified above for manufacture is urgently required for the treatment of patients suffering from_____and that the said drug(s) is/are not available in India.

Place..... Signature

Date..... Medical Superintendent of the Government Hospital or Head of Medical Institution

[Stamp]

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FORM CT-27

(See rules 92, 93, 94 and 95)

PERMISSION TO MANUFACTURE UNAPPROVED NEW DRUG BUT UNDER CLINICAL TRIAL FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR MEDICAL INSTITUTION

Licence Number ……

The Central Licencing Authority hereby grant permission to ……. (Name and full postal address with contact details of the organization) to manufacture the unapproved new drug specified below on the premises situated at ……..……..... (full postal address with contact details of the manufacturing site) for supply to …… (name of the medical officer and address of the Government hospital or medical institution) for the treatment of the patient for the disease …… (Name of the disease).

2. This licence is subject to the conditions prescribed in Chapter XI of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act,1940.

3. This licence shall, unless previously suspended or revoked, be in force for a period of one year from the date specified below:–

4. Details of the new drug to be manufactured

Name:	
Quantity:	

Place: …….

Central Licencing Authority and Stamp

Date: .....

Annexure:

Details of unapproved new drug manufactured:

Serial number	Date of manufacture	Licence number	Name of the unapproved new drug	Quantity manufactured	Manufactured for

Details of record of patient history:

Licence number	Name of the new drug	Patient name	Diagnosis detail with date	Disease name	Dosage schedule

Details of reconciliation of unapproved active pharmaceutical ingredient manufactured:

Date	Name of the unapproved new drug	Licence No.	Quantity manufactured	Quantity supplied	Quantity remained	Supplied to	Quantity – left over or remain unused or got damaged or expired or found of sub-	Action taken

							standard quality	

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*** Write NA where not applicable.**

[F.No.X.11014/10/2017- DRS -Part (1)]

Dr. MANDEEP K. BHANDARI, Jt. Secy.

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ANNEXURE R/2

File No: BIO/CT/20/000095
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

From:

The Drugs Controller General, India
Directorate General of Health Services,

FDA Bhawan Kotla Road,
New Delhi-110002
Dated: 02.08.2020

To

MIs Serum Institute of India Pvt. Ltd.,
212/2, Hadapsar,
Pune-411028..

Subject: Permission for conducting a Phase II/III clinical trial titled "A phase II/III, observer-blind, randomized, controlled study to determine the safety and immunogenicity of COVISHIELD(COVID-19 vaccine) in healthy Indian adults" vide Protocol No: ICMR/SII-COVISHIELD Version No: 2.0 Date: 29 July 2020.- regarding.

Reference: Your Application No. BIO/CT04/FF/2020/20799 dated 24-JUL-2020 on the subject mentioned above.

Sir,

Please refer to your application no. No. BIO/CT04/FF/2020/20799 dated 24-JUL-2020, received by this office on the above subject. Please find enclosed herewith permission to conduct a Phase II/III study in Form CT-06 under the New Drugs and Clinical Trials Rules, 2019 along with the details of new drug and clinical trial sites.

Please acknowledge receipt of the same.

Yours faithfully,

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority

File No: BIO/CT/20/000095

Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FORM CT-06

(See rules 22, 25, 26, 29 and 30)

PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licencing Authority hereby permits M/s Serum Institute of India Pvt. Ltd., 212/2, Off. Soli Poonawalla Road, Hadapsar Pune (India) - 411028 Telephone No.: 020-26602113, 26602378, 26602978 FAX: 020-26993945, 26993921 E-Mail: ssj@seruminstitute.com, to conduct clinical trial of the new drug or investigational new drug as per **Protocol No.: ICMR/SII-COVISHIELD Version No: 2.0 Date: 29 July 2020** in the below mentioned clinical trial sites.

CT No.: CT- 18/2020

2. Details of new drug or investigational new drug and clinical trial site [As per Annexure].

3. This permission is subject to the conditions prescribed in part A of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

VENUGOPAL GIRDHARILAL SOMANI

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority

Place: New Delhi

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

Annexure:

Details of New Drug or Investigational New Drug:

Name of the new drug or investigational new drug:	ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)	
Therapeutic class:	Vaccine	
Dosage form:	Liquid	
Composition:	Each dose of 0.5 mL of vaccine contains:	
	Active ingredient	**Quantity**
	Adeno virus particles (Expressing COVID-19 spike protein)	5×10^{10} virus particles
	Inactive ingredients	
	L-Histidine	10 mM
	Sodium Chloride	35 mM
	Magnesium Chloride	1 mM
	Polysorbate 80	0.1% (w/v)
	Sucrose	7.5% (w/v)
	Ethanol	0.5% (w/v)
	EDTA Disodium Salt	0.1 mM
	Water for Injection	q.s.
Indications:	Prevention of COVID 19 infection	

Details of clinical trial sites-

S. No.	Name and Address of Clinical Trial Site	Ethics Committee details	Name of Principal Investigator
1	Andhra Medical College Maharani Peta, Visakhapatnam, Andhra Pradesh, 530002, India	IEC King George hospital, Maharani Peta Collector Office Junction, Visakhapatnam, Andhra Pradesh, 530002, India ECR/197/Inst/KGH/2013/RR-20	Dr. B. Devi Madhavi
2	JSS Academy of Higher Education and Research Bannimantap Road, Sri Shivarathreeshwara Nagara,Bannimantap A Layout, Bannimantap, Mysore,	Institutional Ethics Committee, 2nd Floor, JSS Medical College, SS Nagar, Mysore – 570015, Karnataka, India ECR/387/Inst/KA/2013/RR-19	Dr Praveen Kulkarni
3	Seth G. S. Medical College and KEM Hospital Acharya Donde Marg, Parel East,Parel, Mumbai	Institutional Ethics Committee Seth GS Medical College and KEM Hospital, Acharya Donde Marg, Parel, Mumbai 400 012, Maharashtra, India ECR/229/Inst/MH/2013/RR-19	Dr Nithya Gogtay
4	KEM Hospital Research Centre Vadu Rural Health	KEM Hospital Research Centre Ethics Committee , TDH building,	Dr. Ashish Bavdekar

	Program, Vadu Budruk, Taluka Shirur, Pune - 412216	3rd Floor, Sardar Moodliar Road, Rasta Peth, 303 Pune-411011, Maharashtra ECR/272/Inst/MH/2013/RR-19	
5	B J Medical College and Sassoon General Hospital Jai Prakash Narayan Road, Pune Railway Station, Pune, 411001	Institutional Ethics Committee of B. J. Government Medical College and Sassoon General Hospital Jai Prakash Narayan Road, Pune Railway Station, Pune, 411001 ECR/280/Inst/Maha/2013/RR-19	Dr. Muralidhar Tambe
6	All India Institute Of Medical Sciences (AIIMS), Jodhpur Department of Community Medicine and Family Medicine, Basni Industrial Area, MIA 2nd Phase, Basni, Jodhpur - 342005	Institutional Ethics Committee 1st floor, Research Block, AIIMS Jodhpur, Basni, Jodhpur - 342005, Rajasthan, India ECR/866/INST/RJ/2016	Dr.Pankaja Raghav
7	Rajendra Memorial Research Institute of Medical Sciences (Indian Council of Medical Research) Department of Health Research, Ministry of Health & Family Welfare, Govt of India, Agamkuan, Patna-800007	Rajendra Memorial Research Institute of medical Sciences RMRIMS Indian Council of medical Research Agamkuan Patna-800007, Bihar, India ECR/480/Inst/BH/2014/RR-17	Dr. Krishna Pandey
8	Institute of Community Medicine, Madras Medical College, Old Central Jail Campus, Park Town, Chennai 600 003	The Institutional Ethics Committee - The Madras Medical Mission, 4-A, Dr. J.J Nagar, Mogappair, Chennai – 600037 ECR/140/Inst/TN/2013/RR-16	Dr. T. S. Selvavinayagam
9	Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education & Research (PGIMER), Sector -12, Chandigarh-160012	Institutional Ethics Committee Room No – 6006, sixth floor, Research Block B, Postgraduate Institute of Medical Education and Research, Sector 12 Chandigarh – 160012, India ECR/25/Inst/CH/2013/RR-16	Dr. Madhu Gupta
10	Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Dhankawadi, Pune- Satara Road, Pune Maharashtra - 411043 India	Institutional Ethics Committee BVDU, Bharati Hospital and Research Centre, Bharati Hospital, Pune - Satara Road Dhankawadi, Pune Maharashtra - 411043 India ECR/313/Inst/MH/2013/RR-19	Dr. Sanjay Lalwani
11	Jehangir Clinical Development Center Pvt.Ltd, Jehangir hospital premises 32, Sasoon, Road	Jehangir Clinical Development Center Pvt.Ltd, Jehangir hospital premises 32, Sasoon, Road Pune, Maharashtra - 411001 India	Dr Kiranjit Singh

	Pune, Maharashtra - 411001 India	ECR/352/Inst/MH/2013/RR-19	
12	Sri Ramachandra Institute for Higher Education and Research (SRIHER) Ramachandra Nagar, Porur Chennai Tiruvallur Tamil Nadu - 600116 India	Institutional Ethics Committee Sri Ramachandra Institute for Higher Education and Research (SRIHER) Ramachandra Nagar, Porur Chennai Tiruvallur Tamil Nadu - 600116 India ECR/203/Inst/TN/2013/RR-19	Dr Ramakrishnan
13	Topiwala National Medical College Nair Hospital, Dr A L Nair Road Mumbai Central, Mumbai, Maharashtra - 400008 India	Institutional Ethics Committee TNMC Nair Hospital, Topiwala National Medical College Nair Hospital, Dr A L Nair Road Mumbai Central, Mumbai, Maharashtra - 400008 India ECR/22/Inst/Maha/2013/RR-19	Dr Renuka Munshi
14	Government Medical College Near Hanuman Nagar Maharashtra - 440003 India	Institutional Ethics Committee, Government Medical College and Hospital, Medical Square Hanuman Nagar, Nagpur, Maharashtra - 440003 India ECR/43/Inst/MH/2013/RR-19	Dr Sushant Meshram
15	Mahatma Gandhi Institute of Medical Sciences Sevagram, Wardha 442102	Institutional Ethics Committee (Department of Pharmacology), Mahatma Gandhi Institute of Medical Sciences, Sevagram Wardha Maharashtra - 442102 India ECR/47/Inst/MH/2013/RR-19	Dr B S Garg
16	All India Institute of Medical Sciences,Director-Department of Pulmonary Medicine & Sleep Disorders, Ansari Nagar, New Delhi - 110029	Institute Ethics Committee All India Institute of Medical Sciences Old OT Block, Room No. 102, AIIMS Hospital Ansari Nagar, New Delhi-29, India ECR/538/Inst/DL/2014/RR-20	Dr Randeep Guleria
17	Nehru Hospital, BRD Medical College, Gorakhpur-273013	Institutional Human Ethical Committee, ICMR-RMRC Gorakhpur, BRD Medical College Campus, Gorakhpur- 273013. EC/NEW/INST/2019/191	Dr Kamran Zaman

In addition to point 3, the permission is subject to following condition(s):

1. The Phase II/III clinical trial should be conducted as per protocol titled "A phase II/III, observer-blind, randomized, controlled study to determine the safety and immunogenicity of COVISHIELD(COVID-19 vaccine) in healthy Indian adults" vide Protocol No: ICMR/SII-COVISHIELD Version No: 2.0 Date: 29 July 2020.
2. The physical/biological characteristics of the vaccine shall be same as that developed by Oxford vaccine and used in the Phase-I/II Clinical trial. The clinical data generated in this trial shall be considered along with the of the data from the Oxford clinical trial outcome.

3. The indication, specification and dose schedule of the applicant vaccine including storage temperature etc., shall be based on the data generated by the collaborators and also the vaccine manufactured in India.
4. The firm is required to constitute a DSMB to review the safety data and submit to CDSCO for proceeding to the immunogenicity cohort study.
5. This permission is subject to the permission from RCGM for carrying out human studies
6. With respect to proposed clinical trial, firm is required to have: ,
   a) Permission in Form CT-11 to manufacture batches of COVISHIELD vaccine .
   b) Permission in CT-17 for import of Oxford vaccine for use in proposed trial .
   c) Permission in CT-14 for labeling & packaging activity at site of M/s Seveillar Clinical Supplies Services Pvt Ltd. Pune.
7. The formulation intended to be used in the clinical trial shall be manufactured as per GMP using validated procedures and shall have ongoing stability studies programme.
8. Firm shall get its batches for clinical trial tested at CDL, Kasauli in parallel due to COVID-19 pandemic situation.

VENUGOPAL GIRDHARILAL SOMANI

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority
Stamp

Place: New Delhi
Date: 02.08.2020

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi

FULL DETAILS (Read-only)

CTRI Number	**CTRI/2020/08/027170** [Registered on: 15/08/2020] **Trial Registered Prospectively**
Last Modified On:	12/06/2021
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Vaccine
Study Design	Randomized, Parallel Group Trial
Public Title of Study	Study to check the safety and immune response of a COVID-19 vaccine in healthy Indian adults.
Scientific Title of Study	A Phase 2/3, Observer-Blind, Randomized, Controlled Study to Determine the Safety and Immunogenicity of Covishield (COVID-19 Vaccine) in Healthy Indian Adults
Secondary IDs if Any Modification(s)	**Secondary ID** / **Registry** ICMR/SII-COVISHIELD Version 4.0 dated 14 Oct 2020 / Protocol Number
Details of Principal Investigator or overall Trial Coordinator (multi-center study)	**Name** **Address** **Phone** **Fax** **Email**
Details Contact Person Scientific Query	Name: Dr Prasad Kulkarni **Address**: Serum Institute of India Private Limited, 212/2, Hadapsar, Pune – 411 028, India Pune MAHARASHTRA 411028 India **Phone**: 00912026602949 **Fax**: 00912026993945 **Email**: drpsk@seruminstitute.com
Details Contact Person Public Query	**Name**: Dr Prasad Kulkarni **Address**: Serum Institute of India Private Limited, 212/2, Hadapsar, Pune – 411 028, India Pune MAHARASHTRA 411028 India **Phone**: 00912026602949 **Fax**: 00912026993945 **Email**: drpsk@seruminstitute.com
Source of Monetary or Material Support Modification(s)	Indian Council of Medical Research (ICMR) V. Ramalingaswami Bhawan, P.O. Box No. 4911 Ansari Nagar, New Delhi - 110029, INDIA Serum Institute of India Private Limited 212/2, Hadapsar, Pune – 411 028, India

Primary Sponsor	**Name**: Serum Institute of India Private Limited **Address**: 212/2, Off Soli Poonawalla Road, Hadapsar, Pune – 411 028, India **Type of Sponsor**: Pharmaceutical industry-Indian
Details of Secondary Sponsor	Name: Indian Council of Medical Research ICMR Address: V. Ramalingaswami Bhawan, P.O. Box No. 4911 Ansari Nagar, New Delhi - 110029, INDIA
Countries of Recruitment	India

Sites of Study
Modification(s)

No of Sites = **14**

Contact Person	Name of Site	Site Address	Phone/Fax/Email
Dr B Devi Madhavi	Andhra Medical College, Visakhapatnam	Department of Community Medicine Andhra Medical College Maharani Peta, Visakhapatnam, Andhra Pradesh 530002, India Visakhapatnam	918912712258 drdevimadhavi@rediffmail.com
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Details of Ethics Committee
Modification(s)

No of Ethics Committees= **14**

Name of Committee	Approval Status
Mahatma Gandhi Institute of Medical Sciences, Institutional Ethics Commitee, Sewagram	Approved
Ethics Committee Jehangir Clinical Development Center Pvt.Ltd, Pune	Approved
Ethics Committee Rajendra Memorial Research Institute of Medical	Approved

Sciences, Patna	
IEC King George Hospital, Visakhapatnam	Approved
Institutional Ethics Committee - TNGMSSH, Chennai	Approved
Institutional Ethics Committee of B. J. Government Medical College and Sassoon General Hospital, Pune	Approved
Institutional Ethics Committee Seth GS Medical College and KEM Hospital, Mumbai.	Approved
Institutional Ethics Committee Sri Ramachandra Institute of Higher Education and Research, Chennai	Approved
Institutional Ethics Committee, BVDU, Pune	Approved
Institutional Ethics Committee, Government Medical College, Nagpur	Approved
Institutional Ethics Committee, JSS Medical College, Mysore	Approved
Institutional Ethics Committee, PGIMER, Chandigarh	Approved
Institutional Ethics Committee, T N Medical College & BYL Nair Hospital, Mumbai	Approved
KEM Hospital Research Centre Ethics Committee, Pune	Approved

Regulatory Clearance Status from DCGI
Modification(s)

Status
Approved/Obtained

Health Condition / Problems Studied

Health Type	Condition
Healthy Human Volunteers	Prevention of COVID-19 infection

Intervention / Comparator Agent
Modification(s)

Type	Name	Details
Intervention	Covishield (SII-ChAdOx1 nCoV-19)	Covishield will be administered as 2 dose schedule on Days 1 and 29 as 0.5 ml dose intramuscularly.
Comparator Agent	Oxford/AZ-ChAdOx1 nCoV-19 vaccine	Oxford/AZ-ChAdOx1 nCoV-19 vaccine will be administered as 2 dose schedule on Days 1 and 29 as 0.5 ml dose intramuscularly.
Comparator Agent	Placebo	Placebo will be administered as 2 dose schedule on Days 1 and 29 as 0.5 ml dose intramuscularly.

Inclusion Criteria

Age From	18.00 Year(s)
Age To	99.00 Year(s)
Gender	Both
Details	1. Healthy adults aged more than or equal to 18 years of either sex. 2. Written informed consent by participants. 3. The participant is resident of the study area and is willing to comply with study protocol requirements. 4. Healthy, as determined by medical history and physical examination. 5. Female participants of childbearing potential must have a negative urine pregnancy test within 24 hours prior to study vaccine administration.

ExclusionCriteria

Details	1. Acute illness with or without fever at the time of study vaccine administration 2. History of laboratory confirmed COVID-19 disease in household contact or close workplace contact 3. IgG seropositivity to SARS-CoV-2 4. History or currently positive for SARS-CoV-2 by RT-PCR 5. History of severe allergic reactions after previous vaccinations or hypersensitivity to any component of study vaccines 6. Any confirmed or suspected condition with impaired/altered function of immune system

Method of Generating Random Sequence	Computer generated randomization
Method of Concealment	Centralized
Blinding/Masking	Participant, Investigator, Outcome Assessor and Date-entry Operator Blinded
Primary Outcome	**Outcome** / **TimePoints** 1. Occurrence of causally related SAEs throughout the study duration following vaccination 2. Ratio of GMTs of anti-S IgG antibodies / 1. Throughout the study duration following vaccination 2. 28 days after the second vaccination
Secondary Outcome	**Outcome** / **TimePoints** Occurrence of serious adverse events (SAEs) / Throughout the study duration following vaccination Occurrence of solicited local and/or systemic adverse events (AEs) / 7 days following each vaccination Occurrence of unsolicited adverse events / 28 days following each vaccination
Target Sample Size	**Total Sample Size=**"1600" **Sample Size from India=**"1600"
Phase of Trial	Phase 2/ Phase 3
Date of First Enrollment (India)	24/08/2020
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**"0" **Months=**"7" **Days=**"0"
Recruitment Status of Trial (Global) Modification(s)	Not Applicable
Recruitment Status of Trial (India)	Completed
Publication Details Modification(s)	Nil
Brief Summary Modification(s)	This is a Phase 2/3, observer-blind, randomised, controlled study in healthy adults in India, for comparison of the safety of COVISHIELD with Oxford/AZ-ChAdOx1 nCoV-19 and Placebo, and immunogenicity with Oxford/AZ-ChAdOx1 nCoV-19 in prevention of SARS CoV-2 infection. A total of 1600 eligible participants of more than or equal to 18 years of age will be enrolled the study. Of these 400 participants will be part of immunogenicity cohort and will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19, respectively. The remaining 1200 participants from safety cohort will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Placebo, respectively.

ANNEXURE R/3

F. No.: BIO/MA/20/000103
Permission no.: MF/BIO/21/000002 dated 03-JAN-2021

FORM CT-23
(*See rules 81, 82, 83 and 84*)

PERMISSION TO MANUFACTURE PHARMACEUTICAL FORMULATION OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licensing Authority hereby grant permission to M/s Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com, Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com to manufacture for sale of pharmaceutical formulation manufactured by a manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this license:

S. No	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site).
1.	Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District,Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com	Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District,Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com **Component** — **Manufacturing facility** Drug substance — • Facility PS2, Building S Drug Product — • Building A, Facility PA1

3. Details of pharmaceutical formulation:

Name of the New drug to be manufactured:	Whole Virion Inactivated Corona Virus Vaccine, [BBV152B]
Dosage form:	Suspension for injection Presentation: single dose glass vial (0.5ml) Route of Administration: Intramuscular
Composition:	Each dose of 0.5ml contains: **Active Ingredients** — **Quantity** Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770) — 6 mcg **Inactive Ingredients** — **Quantity** Aluminium Hydroxide gel equivalent to Al+++ — 250 mcg TLR 7/8 Agonist — 15 mcg 2-Phenoxyethanol (2PE) I.P. — 2.5 mg Phosphate Buffered Saline — q.s. to 0.5 mL * Produced in Vero cells.
Indication:	For active immunization against Corona Virus Disease (COVID-19) for age ≥18 years when administered in two doses interval of day 0 & day 28.
Shelf life with storage condition:	6 months when stored at 2 to 8 °C.

4. This is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act,1940.
5. This permission is for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode.
6. The firm should provide the protocol for rolling out for the restricted use of the vaccine in emergency situation.
7. The firm should provide the updated prescribing information/ Package Insert and Summary of Product Characteristics (SmPC) for Whole Virion Inactivated Corona Virus Vaccine (BBV152B) and also disseminate the necessary information, instructions and educational materials through their website.
8. The firm should submit updated safety, efficacy & immunogenicity data from the ongoing Phase I, II & III clinical trials till the completion of trials as per requirement of New Drugs & Clinical Trials, 2019.
9. The firm should submit safety data including the data on AEFI and AESI, with due analysis, every 15 days for the first two months & monthly thereafter and also as per requirement of New Drugs & Clinical Trials, 2019.
10. The firm should submit Risk management plan.
11. The firm should submit ongoing stability of commercial scale batches (real time and accelerated) of drug substance & drug product.
12. The permission is subject to condition of satisfactory evaluation & lot release by CDL, Kasauli. Further, each batch/lot of Whole Virion Inactivated Corona Virus Vaccine, (BBV152B) shall be released from Central Drugs Laboratory, Kasauli.

VENUGOPAL GIRDHARILAL SOMANI

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

Place: New Delhi
Date: 03-Jan-2021

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

THELANCETID-D-20-06646R2
[PII_REPLACE]
Embargo: February 29, 2021—23:30 (GMT)
Doctopic: Primary Research

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial

Raches Ella, Siddharth Reddy, Harsh Jogdand, Vamshi Sarangi, Brunda Ganneru, Sai Prasad, Dipankar Das, Dugyala Raju, Usha Praturi, Gajanan Sapkal, Pragya Yadav, Prabhakar Reddy, Savita Verma, Chandramani Singh, Sagar Vivek Redkar, Chandra Sekhar Gillurkar, Jitendra Singh Kushwaha, Satyajit Mohapatra, Amit Bhate, Sanjay Rai, Samiran Panda, Priya Abraham, Nivedita Gupta, Krishna Ella, Balram Bhargava, Krishna Mohan Vadrevu

Summary

Background BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine (3 µg or 6 µg) formulated with a toll-like receptor 7/8 agonist molecule (IMDG) adsorbed to alum (Algel). We previously reported findings from a double-blind, multicentre, randomised, controlled phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) and one Algel-only control (no antigen), with the first dose administered on day 0 and the second dose on day 14. The 3 µg and 6 µg with Algel-IMDG formulations were selected for this phase 2 study. Herein, we report interim findings of the phase 2 trial on the immunogenicity and safety of BBV152, with the first dose administered on day 0 and the second dose on day 28.

Methods We did a double-blind, randomised, multicentre, phase 2 clinical trial to evaluate the immunogenicity and safety of BBV152 in healthy adults and adolescents (aged 12–65 years) at nine hospitals in India. Participants with positive SARS-CoV-2 nucleic acid and serology tests were excluded. Participants were randomly assigned (1:1) to receive either 3 µg with Algel-IMDG or 6 µg with Algel-IMDG. Block randomisation was done by use of an interactive web response system. Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to treatment group allocation. Two intramuscular doses of vaccine were administered on day 0 and day 28. The primary outcome was SARS-CoV-2 wild-type neutralising antibody titres and seroconversion rates (defined as a post-vaccination titre that was at least four-fold higher than the baseline titre) at 4 weeks after the second dose (day 56), measured by use of the plaque-reduction neutralisation test ($PRNT_{50}$) and the microneutralisation test (MNT_{50}). The primary outcome was assessed in all participants who had received both doses of the vaccine. Cell-mediated responses were a secondary outcome and were assessed by T-helper-1 (Th1)/Th2 profiling at 2 weeks after the second dose (day 42). Safety was assessed in all participants who received at least one dose of the vaccine. In addition, we report immunogenicity results from a follow-up blood draw collected from phase 1 trial participants at 3 months after they received the second dose (day 104). This trial is registered at ClinicalTrials.gov, NCT04471519.

Findings Between Sept 5 and 12, 2020, 921 participants were screened, of whom 380 were enrolled and randomly assigned to the 3 µg with Algel-IMDG group (n=190) or 6 µg with Algel-IMDG group (n=190). Geometric mean titres (GMTs; $PRNT_{50}$) at day 56 were significantly higher in the 6 µg with Algel-IMDG group (197·0 [95% CI 155·6–249·4]) than the 3 µg with Algel-IMDG group (100·9 [74·1–137·4]; p=0·0041). Seroconversion based on $PRNT_{50}$ at day 56 was reported in 171 (92·9% [95% CI 88·2–96·2] of 184 participants in the 3 µg with Algel-IMDG group and 174 (98·3% [95·1–99·6]) of 177 participants in the 6 µg with Algel-IMDG group. GMTs (MNT_{50}) at day 56 were 92·5 (95% CI 77·7–110·2) in the 3 µg with Algel-IMDG group and 160·1 (135·8–188·8) in the 6 µg with Algel-IMDG group. Seroconversion based on MNT_{50} at day 56 was reported in 162 (88·0% [95% CI 82·4–92·3]) of 184 participants in the 3 µg with Algel-IMDG group and 171 (96·6% [92·8–98·8]) of 177 participants in the 6 µg with Algel-IMDG group. The 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations elicited T-cell responses that were biased to a Th1 phenotype at day 42. No significant difference in the proportion of participants who had a solicited local or systemic adverse reaction in the 3 µg with Algel-IMDG group (38 [20·0%; 95% CI 14·7–26·5] of 190) and the 6 µg with Algel-IMDG group (40 [21·1%; 15·5–27·5] of 190) was observed on days 0–7 and days 28–35; no serious adverse events were reported in the study. From the phase 1 trial, 3-month post-second-dose GMTs (MNT_{50}) were 39·9 (95% CI 32·0–49·9) in the 3µg with Algel-IMDG group, 69·5 (53·7–89·9) in the 6 µg with Algel-IMDG group, 53·3 (40·1–71·0) in the 6 µg with Algel group, and 20·7 (14·5–29·5) in the Algel alone group.

Interpretation In the phase 1 trial, BBV152 induced high neutralising antibody responses that remained elevated in all participants at 3 months after the second vaccination. In the phase 2 trial, BBV152 showed better reactogenicity and

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For the Hindi translation of the abstract see Online for appendix 1

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safety outcomes, and enhanced humoral and cell-mediated immune responses compared with the phase 1 trial. The 6 µg with Algel-IMDG formulation has been selected for the phase 3 efficacy trial.

Funding Bharat Biotech International.

Introduction

For more on the **WHO Coronavirus Disease Dashboard** see https://covid19.who.int/

The novel human coronavirus SARS-CoV-2 has spread worldwide. To date, 194 vaccine candidates are being developed to prevent COVID-19.[1] Vaccines from multiple manufacturers will be needed to address the global need for SARS-CoV-2 vaccines. Several such vaccines (inactivated, viral vector, or mRNA) have received emergency use authorisation for immunisation of health-care workers and at-risk individuals.[2–5] There is currently an insufficient supply of vaccines, and the mRNA-based vaccines have cold chain hurdles that countries need to overcome.

BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor (TLR) 7/8 agonist molecule adsorbed to alum (Algel-IMDG). BBV152 is stored between 2°C and 8°C, which will ease immunisation cold chain requirements.

Preclinical studies in mice, rats, and rabbits showed appropriate safety profiles and humoral and cell-mediated responses.[6] Live viral challenge protective efficacy studies in hamsters and non-human primates showed rapid viral clearance in the lower and upper respiratory tracts, and the absence of lung pathology after viral challenge.[7,8]

We previously reported interim findings from a double-blind, randomised, phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, and 6 µg with Algel) and one Algel only control (without antigen).[9] This phase 1 trial was done with the intention of selecting two formulations. Based on acceptable safety outcomes, and humoral and cell-mediated responses, the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations were selected for progression to a phase 2 trial. The decision to change the dosing schedule from a

Research in context

Evidence before this study

We searched PubMed on Jan 23, 2021, using the search terms "SARS-CoV-2", "COVID-19", "vaccine", and "clinical trial". We searched for research articles published from database inception to the date of the search, with no language restrictions. We found 12 clinical trials of COVID-19 mRNA, adenovirus vectored, protein subunit, and inactivated virus vaccines. A preferred characteristic of any COVID-19 vaccine candidate is its ability to induce T-helper-1 (Th1) responses. Whole-virion inactivated vaccines are mostly developed with alum (Algel) as the adjuvant. The response generated by alum is primarily biased to Th2. Clinical trial results from two other inactivated virus vaccines (manufactured by Sinovac and Sinopharm) reported humoral responses but minimal cell-mediated responses. Bharat Biotech developed a Vero cell-based whole-virion inactivated SARS-CoV-2 vaccine (BBV152), formulated with alum and a toll-like receptor 7/8 agonist, producing a Th1-skewed response. BBV152 showed protection in non-human primate and hamster challenge models. Data from a phase 1 study suggested adequate safety and immunogenicity findings. In January 2021, serum samples taken from 38 participants in the 6 µg with Algel-IMDG group at 4 weeks after the second dose (day 56) in the phase 2 trial were found to effectively neutralise a SARS-CoV-2 variant of concern (B.1.1.7 or 20B/501Y. V1).

Added value of this study

We report preliminary analyses for the immunogenicity and safety of BBV152 in 380 vaccinated adults and adolescents. BBV152 led to enhanced immune responses and induced T-cell responses that were biased to Th1. Due to the difference in dosing regimens between phase 1 (two doses given 2 weeks apart) and phase 2 (two doses given 4 weeks apart) trials, neutralisation responses were significantly higher in the phase 2 trial than in the phase 1 trial. Immunological differences between men and women, and across age groups were not observed. Overall, both 3 µg with Algel-IMDG and 6 µg with Algel-IMDG vaccine groups had similar safety outcomes. Follow-up data from the phase 1 trial shows that BBV152 induces durable humoral and cell-mediated immunity at 3 months after the second dose (day 104).

Implications of all the available evidence

Humoral immune responses from other inactivated SARS-CoV-2 vaccine candidates are consistent with the findings of this study. However, this is the only study of an inactivated COVID-19 vaccine candidate to report a thorough evaluation of cell-mediated responses. The 6 µg with Algel-IMDG formulation has been selected for the phase 3 efficacy trial. BBV152 (developed using a well established manufacturing platform) was safe, immunogenic (persisting for 3 months), and can be stored at 2–8°C, which is compatible with the immunisation cold chain requirements of most countries. Follow-up studies to assess efficacy and immune responses in older adults and in people with comorbidities are underway.

14-day interval between the first and second doses (phase 1 trial), to a 28-day interval between the two doses (phase 2 trial) was based on ensuring commonality with other licensed COVID-19 vaccines. In the phase 1 trial, no difference in the safety and immunogenicity between the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups was observed. In this phase 2 trial, the inclusion of a placebo group was not planned. Our objective was to increase the sample size to establish whether there are differences in immunogenicity between the 3 µg with Agel-IMDG and 6 µg with Algel-IMDG groups. Therefore, no control or Algel alone group was included in this study.

Herein, we report interim findings from the phase 2 trial on the immunogenicity and safety of 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations of BBV152. Additionally, this paper reports follow-up immunological results from the phase 1 trial at 3 months after participants received the second dose (day 104).

Methods

Study design and participants

This is a randomised, multicentre, phase 2 clinical trial to evaluate the immunogenicity and safety of the whole-virion inactivated SARS-CoV-2 vaccine BBV152 in healthy male and female volunteers at nine hospitals across nine states in India. Participants were aged 12–65 years at the time of enrolment. At the screening visit, participants were tested using both SARS-CoV-2 nucleic acid and serology tests, which were done at a central laboratory (Dr Dangs Laboratory, New Delhi, India) using commercially available assays. If individuals were positive for either test, they were excluded from the trial. The median time between the screening visit and vaccination visit was 3 days (range 2–4). Individuals aged older than 65 years, pregnant or lactating women, and individuals with comorbidities were excluded. All study-related activities and the opportunity to decline or withdraw from the study were explained to participants. All participants were screened for eligibility on the basis of their health status, including their medical history, vital signs, and physical examination results, and were enrolled after providing signed and dated informed consent forms. Details of the inclusion and exclusion criteria can be found in the protocol (appendix 2 pp 50–51).

The trial was approved by the National Regulatory Authority (India) and the respective ethics committees of each participating hospital and was conducted in compliance with all International Council for Harmonization Good Clinical Practice guidelines.

Randomisation and masking

The master randomisation list was uploaded to the interactive web response system, which contained the randomisation number and intended allocation. A central depot manager uploaded the kit numbers to the respective sites. At the site-level, the system would set the randomisation number and the allotment of the kit without displaying the true group allocation; the system would allocate the same treatment group for the second visit. A block size of four was used to randomly assign (1:1) participants to either the 3 µg with Algel-IMDG group or the 6 µg with Algel-IMDG group. An unmasked contract research organisation (Sclin Soft Technologies, Hyderabad, India) generated the master randomisation code, and dispatched and labelled the vaccine vials.

Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to the treatment group allocation (excluding the unmasked contract research organisation). Participants were assigned a computer-generated randomisation code that maintained masking. A masked study nurse prepared and administered the vaccines. Each vial contained a unique code that ensured appropriate masking.

Procedures

BBV152 (manufactured by Bharat Biotech) is a whole-virion β-propiolactone-inactivated SARS-CoV-2 vaccine. The NIV-2020-770 strain was isolated from a patient with COVID-19, sequenced at the Indian Council of Medical Research-National Institute of Virology, and provided to Bharat Biotech.[10] Biosafety level 3 manufacturing facilities and a well established Vero cell manufacturing platform aided the rapid development of BBV152. The NIV-2020-770 strain contains the Asp614Gly mutation, which is characterised by an aspartic acid to glycine shift at amino acid position 614 of the spike protein.[10] Studies suggest that the mutation is associated with higher viral loads in patients and animal models compared with the wild-type strain[11] and that NIV-2020-770 is considered to be the dominant strain in the pandemic.[12]

The candidates were formulated with the Algel-IMDG adjuvant, which is an imidazoquinoline class molecule (TLR 7/8 agonist) adsorbed onto Algel. After confirming their eligibility, participants were randomly assigned to the two groups. Both vaccines were stored at 2–8°C in a single-use glass vial. The appearance, colour, and viscosity of the two formulations were identical.

Vaccines were provided as a sterile liquid that was injected through an intramuscular route (deltoid muscle) at a volume of 0·5 mL per dose in a two-dose regimen on day 0 and day 28. Each glass vial contained a single dose of one of the vaccine formulations and required no additional dilution steps, therefore, no on-site dose preparation was required. No prophylactic medication (ibuprofen or acetaminophen) was prescribed either before or after vaccination. The follow-up visits were scheduled on days 42, 56, 118, and 208 after vaccination for blood collection.

Anti-IgG responses against the spike (S1) glycoprotein, receptor-binding domain (RBD), and nucleocapsid protein

See Online for appendix 2

of SARS-CoV-2 were assessed by ELISA (Syngene, Bangalore, India), and are expressed as geometric mean titres (GMTs). Wild-type virus neutralising antibody titres in serum samples were analysed with a microneutralisation test (MNT_{50}) and a plaque-reduction neutralisation test ($PRNT_{50}$) at Bharat Biotech in a masked manner.MNT_{50} and $PRNT_{50}$ were developed in-house. Seroconversion was defined as a post-vaccination titre at least four-fold higher than the pre-vaccination titre. To ensure the validity of our assay, an arbitrary number of serum samples (n=40) were selected at random and tested by $PRNT_{50}$ at the National Institute of Virology.

See Online for appendix 3

Due to the absence of established SARS-CoV-2-specific correlates of protection, to compare vaccine-induced immune responses with those elicited by natural SARS-CoV-2 infections, 50 convalescent serum samples (collected 1–2 months after a nucleic acid test-based diagnosis) were tested by $PRNT_{50}$ and MNT_{50}. These serum samples were collected from self-reported symptomatic (n=35) and asymptomatic (n=15) adult (age-range not known) patients with COVID-19, and were provided by the National Institute of Virology (Pune, India). For symptomatic patients, ascertainment of severity grading and the requirement for supplemental oxygen was not available.

Cell-mediated responses were assessed in a subset of participants at three sites on day 42 and day 56. The contract research organisation generated a random code containing randomisation numbers, which was provided to the staff to identify this subset of participants. Blood (3–5 mL) was collected from participants who consented to have additional blood volume collected on day 42. Serum was used to evaluate Th1-dependent and Th2-dependent antibody isotypes, and peripheral blood mononuclear cells (PBMCs) were used to assess Th1 and Th2 cytokines. PBMCs were collected from 58 participants (29 from each group). Ten pre-vaccination samples (five from each group) collected on day 0 served as the control. Formal sample size estimations for cell-mediated responses were not done. PBMCs collected on day 42 were used to assess Th1 (interferon-γ [IFNγ], tumour necrosis factor-α [TNFα], and IL-2) and Th2 (IL-5, IL-10, and IL-13) cytokines using a Luminex multiplex assay (Luminex Corporation, Austin, TX, USA) at Indoor Biotechnologies (Bangalore, India).

PBMCs collected on day 56 were used to assess Th1 and Th2 cytokines using a cytokine bead array multiplex assay (CBA Kit, BD Biosciences, New Jersey, USA).These tests were done at Bharat Biotech.

PBMCs from a subset of randomly selected participants who consented to the additional blood volume were collected on day 104 of the phase 1 trial, and used to assess T-cell memory responses ($CD4^+CD45RO^+$ T cells and $CD4^+CD45RO^+CD27^+$ T cells) at Bharat Biotech. Wild-type virus neutralisation assays (GMTs and seroconversion [MNT_{50}] assays) were done in phase 1 participants at day 104. After antigen stimulation of these PBMCs, culture supernatants were collected on day 3 to assess cytokines and secreted SARS-CoV-2 IgG antibodies (by ELISA) on day 6. All samples were analysed in a masked manner. The details of all assay methods can be found in appendix 3 (pp 3–4).

Outcomes

The primary outcome was SARS-CoV-2 wild-type neutralising antibody titres and seroconversion rates at 4 weeks after the second dose (day 56).

A key secondary outcome was the number and proportion of participants with solicited local and systemic reactogenicity. Participants were observed for 2 h post-vaccination to assess reactogenicity. They were instructed to record local and systemic reactions within 7 days (days 0–7 and days 28–35) post-vaccination using a paper-based memory aid. The memory aid contained fields for symptom onset, severity, time to resolution, and concomitant medications, and participants were instructed to complete the form daily. The form was collected during the next visit to the site. Routine telephone calls were scheduled following the first 7 days after each vaccination. Solicited local adverse events were pain and swelling at the injection site, and systemic adverse events were fever, fatigue or malaise, myalgia, body aches, headache, nausea or vomiting, anorexia, chills, generalised rash, and diarrhoea. All unsolicited adverse events were reported by participants throughout the study. The grading scale for most adverse events was based on the US Food and Drug Administration (FDA) document for the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Adverse events for which grading was not described in the FDA guidance document were graded by use of the Common Terminology Criteria for Adverse Events. Adverse events were graded according to severity score (mild, moderate, or severe) and whether they were related or unrelated to the investigational vaccine, as detailed in the protocol (appendix 2).

Statistical analysis

We calculated that 171 participants per group were required for 90% power to detect a significant difference between GMTs in two equally sized groups, assuming the $\log_{10}$ (titre) is normally distributed with an SD of 0·5, the true GMT ratio is 1·5, and the groups are compared with a two-sample *t* test on $\log_{10}$ (titre) at a two-sided 5% significance level. Assuming a 10% loss of participants due to drop-out during the study, the sample size was calculated as 190 participants in each group. Sample size was calculated by use of PASS 13 software (Number Cruncher Statistical Systems, Kaysville, UT, USA).

The primary outcome was assessed in all participants who received two doses of the vaccine. Safety was assessed in all participants who received at least one dose of the vaccine. Safety endpoints are described as frequencies. GMTs with 95% CIs are presented for immunological endpoints. For continuous variables (those with

<20 observations), medians and IQRs are reported. The exact binomial calculation was used for the CI estimation of proportions. Wilson's test was used to test differences in proportions. CI estimation for the GMT was based on the $\log_{10}$ (titre) and the assumption that the $\log_{10}$ (titre) was normally distributed. GMTs were compared with *t* tests using the means of the $\log_{10}$ (titre). Significance was set at p<0·05 (two-sided).

This preliminary report presents results regarding immunogenicity (days 0–56) and safety outcomes (days 0–42). Descriptive and inferential statistics were assessed using SAS, version 9.2.

The trial is registered at ClinicalTrials.gov, NCT04471519.

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of this report or the statistical report, but was involved in study design. Data cleaning and analysis was done by the third party contract research organisation (Sclin Soft Technologies). Masked laboratory assessments were done at the respective laboratories, and masked datasheets were sent to the contract research organisation for decoding and analysis. The unmasked randomisation list was not shared with the study sponsor.

Results

Between Sept 5 and 12, 2020, 921 potential participants were screened, 380 of whom were enrolled and randomly assigned to either the 3 µg with Algel-IMDG group (n=190) or the 6 µg with Algel-IMDG group (n=190; figure 1). Among the 541 individuals who were initially screened but excluded, 48 had positive nucleic acid tests and 123 had positive serology tests for SARS-CoV-2. Due to competitive recruitment, 190 individuals who were screened and found to be eligible were not enrolled. Other notable exclusions were due to inconclusive RT-PCR results (n=168). The retention rates at day 56 were 97% (184 of 190 participants) in the 3 µg with Algel-IMDG group and 93% (177 of 190 participants) in the 6 µg with Algel-IMDG group. The demographic characteristics of participants are shown in table 1.

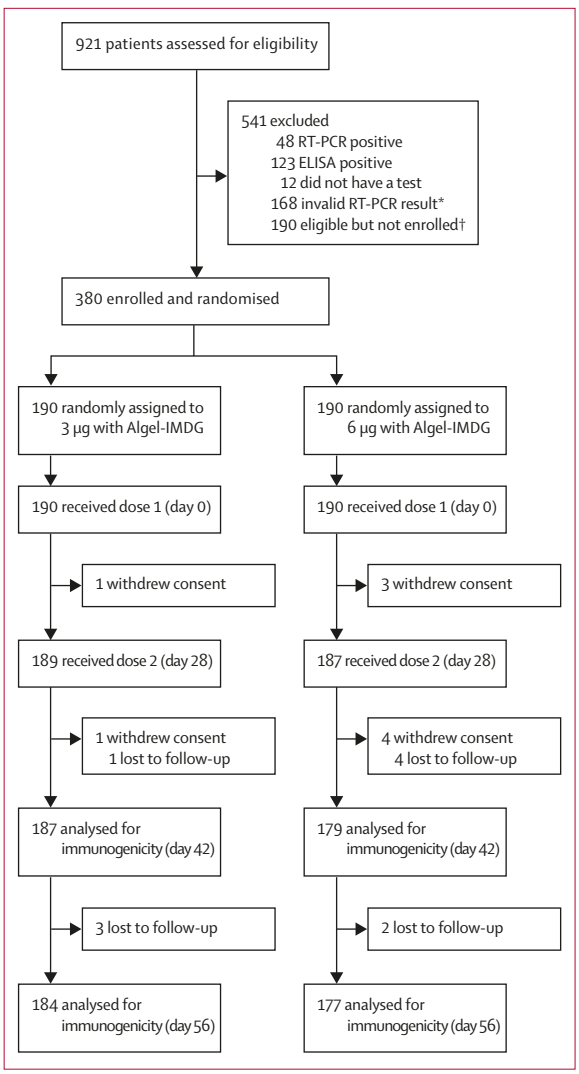

Figure 1: **Trial profile**
*Caused by cold chain excursions during transport of the nasopharyngeal swabs from the field site to the central laboratory. †Due to competitive recruitment, all sites were screening participants individually; therefore, there was an excess of eligible participants who were not enrolled because the recruitment target was met.

GMTs ($PRNT_{50}$) at day 0 were 0·1 (95% CI 0·1–0·1) in both groups, increasing to 100·9 (74·1–137·4) in the 3 µg with Algel-IMDG group and 197·0 (155·6–249·4) in the 6 µg with Algel-IMDG group at day 56 (figure 2A). The GMT ($PRNT_{50}$) at day 56 was significantly higher in the 6 µg with Algel-IMDG group than in the 3 µg with Algel-IMDG group (p=0·0041), and was not significantly different to the GMT ($PRNT_{50}$) observed in convalescent serum collected from patients who had recovered from COVID-19 (p=0·54). Seroconversion based on $PRNT_{50}$ at day 56 was reported in 171 (92·9% [95% CI 88·2–96·2] of 184 participants in the 3 µg with Algel-IMDG group and 174 (98·3% [95·1–99·6]) of 177 participants in the 6 µg with Algel-IMDG group (figure 2B).

GMTs (MNT_{50}) at day 56 were 92·5 (95% CI 77·7–110·2) in the 3 µg with Algel-IMDG group and 160·1 (135·8–188·8) in the 6 µg with Algel-IMDG group (figure 2C). Seroconversion based on MNT_{50} at day 56 was reported in 162 (88·0% [95% CI 82·4–92·3]) of 184 participants in the 3 µg with Algel-IMDG group and 171 (96·6% [92·8–98·8]) of 177 participants in the 6 µg with Algel-IMDG group (figure 2D; appendix 3, p 6). The $PRNT_{50}$ and MNT_{50} GMTs at day 56 were significantly higher in the 6 µg with Algel-IMDG group than the 3 µg with Algel-IMDG group. No differences in the GMTs ($PRNT_{50}$) were observed in a subset of paired serum samples from both groups (20 samples from each group) analysed at the National Institute of Virology and Bharat

Biotech on day 42 (2 weeks after the second vaccination; appendix 3, p 13). Seroconversion rates and GMTs across three age groups (≥12 to <18 year, ≥18 to <55 year, and ≥55 to ≤65 year groups) and between both sexes were similar, but only small numbers of participants were included in the youngest and oldest age groups (appendix 3, p 7).

	3 µg with Algel-IMDG (n=190)	6 µg with Algel-IMDG (n=190)
Age, years		
Median	34·0 (26·0–41·8)	35·0 (27·0–44·0)
≥12 to <18	10 (5%)	4 (2%)
≥18 to <55	173 (91%)	176 (93%)
≥55 to ≤65	7 (4%)	10 (5%)
Sex		
Female	50 (26%)	45 (24%)
Male	140 (74%)	145 (76%)
Body-mass index*, kg/m²	25·1 (3·4)	24·9 (2·8)

Data are median (IQR), n (%), or mean (SD). The intention-to-treat population included all participants who received at least one dose. *Calculated by the participant's weight (kg) divided by the square of their height (m), measured at the time of screening.

Table 1: **Demographics of participants in the intention-to-treat population**

IgG antibody titres (GMTs) to all epitopes (spike glycoprotein, receptor-binding domain, and nucleocapsid protein) were detected after the administration of both doses (table 2). Anti-spike glycoprotein IgG GMTs at day 56 were 10413·9 (95% CI 9142·4–11862·2) in the 3 µg with Algel-IMDG group and 9541·6 (8245·9–11041·0) in the 6 µg with Algel-IMDG group. Both the 3 µg and 6 µg with Algel-IMDG groups showed similar anti-spike glycoprotein, anti-receptor-binding domain, and anti-nucleocapsid protein GMTs. At day 42, the anti-spike isotype mean ratios (IgG1/IgG4) were 2·4 (95% CI 1·9–2·9) in the 3 µg with Algel-IMDG group and 2·2 (1·7–2·6) in the 6 µg with Algel-IMDG group.

The Th1/Th2 cytokine ratio indicated bias to a Th1 cell response at day 42 (figure 3A). Th2 responses were detected at minimal levels in both vaccine groups, as shown by IL-5, IL-10, and IL-13 levels (figure 3B). We observed a significant increase in the levels of Th1 cytokines, IFNγ, IL-2, and TNFα, on day 56 compared with

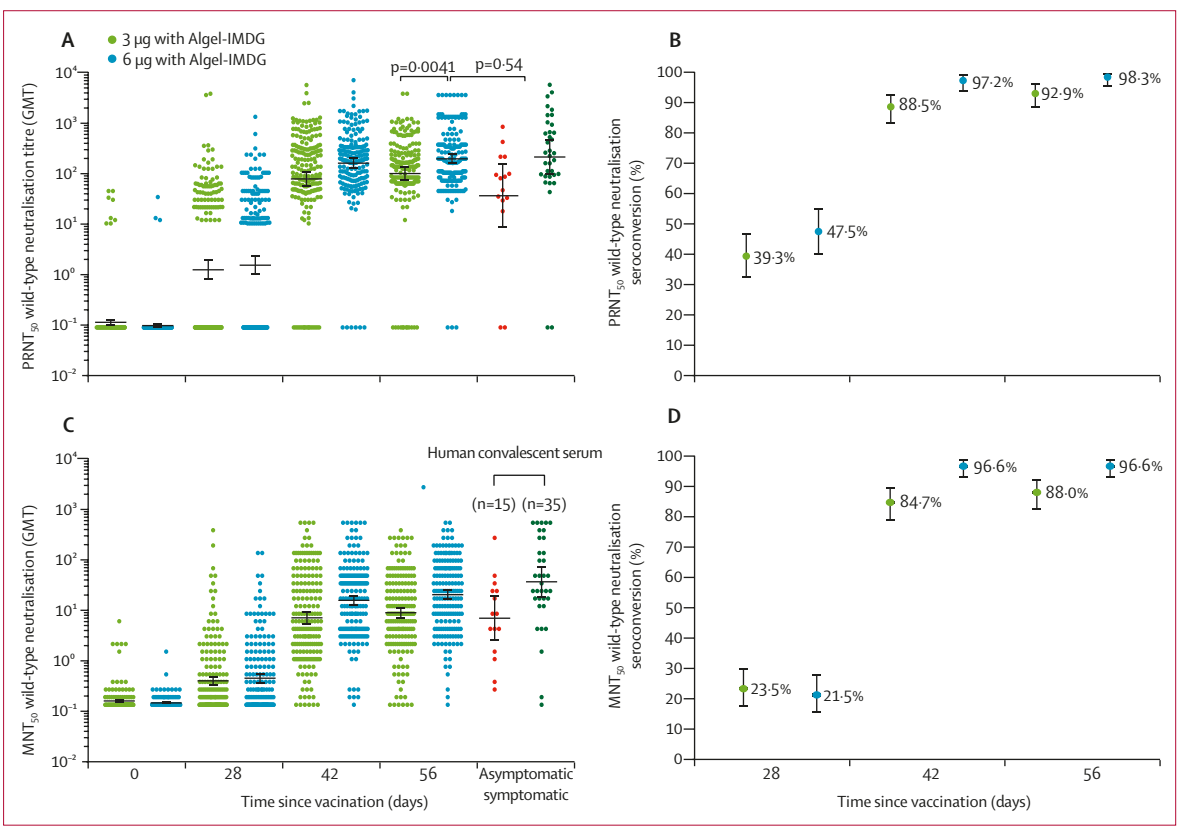

Figure 2: **SARS-CoV-2 wild-type $PRNT_{50}$ GMTs (A), and seroconversion rates (B), and wild-type MNT_{50} GMTs (C) and seroconversion rates (D)**
SARS-CoV-2 wild-type $PRNT_{50}$ and MNT_{50} GMTs at baseline (day 0), 4 weeks after the first vaccination (day 28), 2 weeks after the second vaccination (day 42), and 4 weeks after the second vaccination (day 56) in the 3 µg with Algel-IMDG (n=190) and 6 µg (n=190) with Algel-IMDG groups are shown. Seroconversion rates were defined by the proportion of post-vaccination titres that were at least four-fold higher than baseline. In A and C, the human convalescent sera panel included specimens from participants with PCR-confirmed symptomatic and asymptomatic COVID-19 obtained at least 30–60 days after diagnosis (50 samples); dots represent individual datapoints, the horizontal bars show the GMTs, and the error bars represent the 95% CIs. In B and D, the dots represent the seroconversion rates and error bars represent 95% CIs. $PRNT_{50}$=plaque-reduction neutralisation test. GMT=geometric mean titre. MNT_{50}=microneutralisation assay.

	Geometric mean titre (95% CI)		Seroconversion rate* (95% CI)	
	3 µg with Algel-IMDG	6 µg with Algel-IMDG	3 µg with Algel-IMDG	6 µg with Algel-IMDG
Anti-spike glycoprotein IgG				
Day 0	500·0 (500·0–500·0)	500·0 (500·0–500·0)	..	..
Day 28	2574·2 (2228·9–2973·1)	2240·5 (1942·4–2584·5)	71·2% (64·1–77·6)	65·0% (57·5–72·0)
Day 42	11528·8 (10 002·7–13 287·8)	10040·0 (8667·0–11 630·5)	98·4% (95·3–99·7)	98·3% (95·1–99·7)
Day 56	10413·9 (9142·4–11 862·2)	9541·6 (8245·9–11 041·0)	98·4% (95·3–99·7)	96·6% (92·8–98·8)
Anti-receptor binding domain IgG				
Day 0	500·0 (500·0–500·0)	500·0 (500·0–500·0)	..	..
Day 28	1962·7 (1726·2–2231·6)	2031·6 (1777·3–2322·3)	58·7% (51·2–65·9)	58·2% (50·6–65·6)
Day 42	5572·3 (4897·5, 6339·9)	4980·8 (4366·7, 5681·3)	94·0% (89·6, 97·0)	93·2% (88·5, 96·5)
Day 56	5874·0 (5194·8, 6642·0)	5558·0 (4859·9, 6356·5)	96·2% (92·3, 98·5)	94·4% (89·9, 97·3)
Anti-nucleocapsid protein IgG				
Day 0	500·0 (500·0–500·0)	500·0 (500·0–500·0)	..	..
Day 28	2734·1 (2375·1–3147·5)	2490·4 (2161·7–2869·2)	72·3% (65·2–78·6)	71·2% (63·9–77·7)
Day 42	8957·2 (7778·6–10314·3)	9211·2 (7939·3–10 686·8)	97·3% (93·8–99·1)	95·5% (91·3–98·0)
Day 56	8626·0 (7528·6–9883·4)	8754·0 (7589·4–10 097·4)	97·3% (95·3–100·0)	96·6% (92·8–98·8)

ELISA results at baseline (day 0), 4 weeks after the first vaccination (day 28), 2 weeks after the second vaccination (day 42), and 4 weeks after the second vaccination (day 56) for the 3 µg with Algel-IMDG and the 6 µg with Algel-IMDG groups are shown. The number of participants in the 3 µg with Algel-IMDG group included in the immunogenicity analysis was 190 on day 0, 189 on day 28, 187 on day 42, and 184 on day 56. The number of participants in the 6 µg with Algel-IMDG group included in the immunogenicity analysis was 190 on day 0, 187 on day 28, 179 on day 42, and 177 on day 56. The cutoff for detectable antibodies was 1/500. Endpoint titre dilution for days 28, 42, and 56 sera samples were established with baseline (day 0) and interpolated from the raw optical density data of the corresponding day 0 sample. The cutoff (mean ±3 SD) for day 0 was calculated considering the absorbance of all sera dilutions (1/500 to 1/32 000) tested, except the lowest dilution (1/500). *Defined as a post-vaccination IgG titre that was at least four-fold higher than the baseline titre.

Table 2: **SARS-CoV-2 IgG titres against the spike glycoprotein, receptor-binding domain, and nucleocapsid protein**

day 0 (p<0·0001), as measured with the Luminex multiplex assay (appendix 3, p 12).

Solicited local adverse reactions after dose 1 (days 0–7) were reported in nine (4·7% [95% CI 2·2–8·8]) of 190 participants in the 3 µg with Algel-IMDG group and eight (4·2% [1·8–8·1]) of 190 participants in the 6 µg with Algel-IMDG group (table 3). Solicited systemic adverse reactions after dose 1 were reported in nine (4·7% [2·2–8·8]) participants in the 3 µg with Algel-IMDG group and 14 (7·4% [4·1–12·1]) participants in the 6 µg with Algel-IMDG group. Solicited local adverse reactions after dose 2 (days 28–35) were reported in eight (4·2% [1·8–8·1]) participants in the 3 µg with Algel-IMDG group and seven (3·7% [1·6–7·7]) participants in the 6 µg with Algel-IMDG group. Solicited systemic adverse reactions after dose 2 were reported in 12 (6·3% [3·3–10·8]) participants in the 3 µg with Algel-IMDG group and 11 (5·8% [3·0–10·1]) participants in the 6 µg with Algel-IMDG group (table 3; unsolicited adverse events are included in appendix 3, p 9).

No association between the dose of vaccine and the number of adverse events was observed. After both doses, the most common solicited adverse events were injection site pain, reported in five (2·6% [95% CI 0·9–6·0]) of 190 participants in the 3 µg with Algel-IMDG group and six (3·2% [1·2–6·8]) of 190 participants in the 6 µg with Algel-IMDG group. Most adverse events were mild (69 [89%] of 78 participants) and resolved within 24 h of onset. At 7 days after the second dose, solicited local and systemic adverse reactions were reported in 38 (20·0% [14·7–26·5]) of 190 participants in the 3 µg with Algel-IMDG group and 40 (21·1% [15·6–27·7]) of 190 participants in the 6 µg with Algel-IMDG group.

In the phase 1 trial, 97 (97%) of 100 participants in the 3 µg with Algel-IMDG group, 95 (95%) of 100 participants in the 6 µg with Algel-IMDG group, 92 (92%) of 100 participants in the 6 µg with Algel group, and 69 (92%) of 75 participants in the Algel-only control group were followed up to day 104 (3 months after the second dose). GMTs (MNT_{50}) at day 104 were 39·9 (95% CI 32·0–49·9) in the 3 µg with Algel-IMDG group, 69·5 (53·7–89·9) in the 6 µg with Algel-IMDG group, 53·3 (40·1–71·0) in the 6 µg with Algel group, and 20·7 (14·5–29·5) in the Algel-only control group (figure 4A). Seroconversion based on MNT_{50} was reported in 72 (73·5% [95% CI 63·6–81·9]) participants in the 3 µg with Algel-IMDG group, 76 (81·1% [71·4–88·1]) participants in the 6 µg with Algel-IMDG group, and 68 (73·1% [62·9–81·8]) participants in the 6 µg with Algel group (figure 4B). GMTs in the 6 µg with Algel-IMDG group were significantly higher than the 3 µg with Algel-IMDG group (appendix 3, p 7). There were no significant differences in GMTs between day 42 (2 weeks after the second dose) and 104 (3 months after the second dose) across the vaccine groups (appendix 3, p 7). Post-hoc analyses of MNT_{50} wild-type neutralising antibody responses in phase 1 and phase 2 participants in the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups, showed that GMTs were significantly higher in phase 2 participants (at day 56)

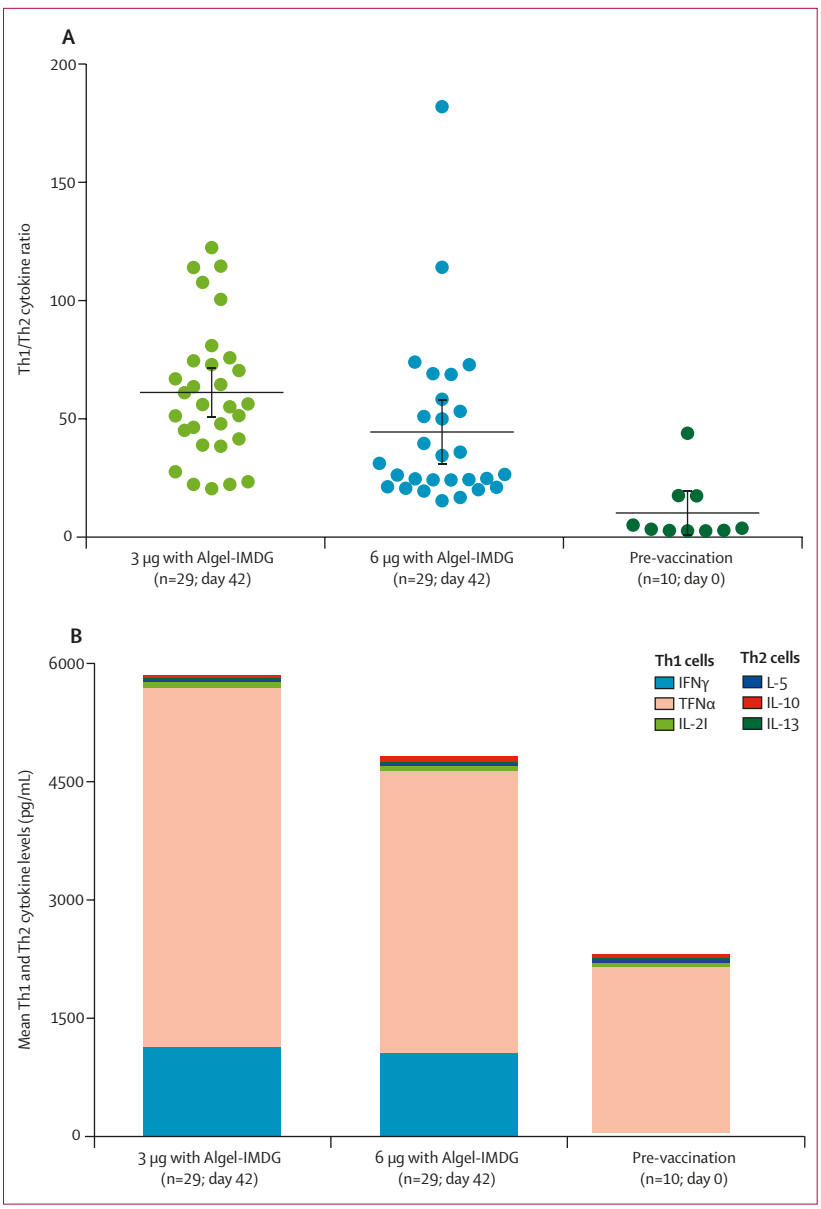

Figure 3: **Th1/Th2 cytokine ratios (A) and mean Th1 and Th2 cytokine levels (B) at day 42 in phase 2 participants**
In A and B, cell-mediated responses in blood samples from 58 participants (29 each from the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups), with proliferative responses to vaccination at 2 weeks after the second dose (day 42), and in ten control participants (five pre-vaccination samples from each group) are shown. In A, the Th1/Th2 ratio was calculated by the sum of IFNγ plus IL-2 cytokine levels divided by the sum of IL-5 plus IL-13 cytokine levels; horizontal bars show the mean ratios and error bars show the 95% CIs. In B, mean cytokine levels in the cell culture supernatants obtained from PBMCs stimulated with SARS-CoV-2 peptides are shown; Th1 (IFNγ, IL-2, and TNFα) and Th2 (IL-5, IL-13, and IL-10) cytokines are represented by stacked bars. Th=T-helper. IFNγ=interferon-γ. TNFα=tumour necrosis factor-α. IL=interleukin.

than in phase 1 participants (at day 42) at 4 weeks after receiving the second dose (figure 4C). At 4 weeks after the second dose of 6 µg with Algel-IMDG, the phase 1–2 GMT (MNT_{50}) ratio was 1·9 (95% CI 1·5–2·6).

PBMCs from a subset of phase 1 participants at one site were collected to evaluate T-cell memory responses at day 104. Formulations with Algel-IMDG generated a T-cell memory response, as shown by an increase in the frequency of effector memory $CD4^+CD45RO^+$ T cells and $CD4^+CD45RO^+CD27^+$ T cells compared with pre-vaccination (day 0) samples (figure 4D, E). Samples from Algel-alone recipients also showed a T-cell memory response. We also detected secreted IgG antibodies in the cell culture supernatant by ELISA, and the antibody titres ranged from neat (undiluted) to 1/64 (appendix 3 p 8). Further effector function of activated and differentiated T cells was shown by the levels of Th1 cytokines (appendix 3 p 8).

In phase 2 participants, nine (33%) of 27 unsolicited adverse events were reported to be related to the vaccine, as judged by a masked investigator. No significant difference in the number of unsolicited adverse events was observed between the groups (appendix 3 p 9). Severity grading scales for adverse events and the evaluation of adverse events related to the vaccine are described in appendix 3 (pp 10–11). No symptomatic SARS-CoV-2 infections were reported to the site investigators (via follow-up telephone calls or site visits) between days 0 and 118 (a scheduled visit) in phase 2 participants. However, illness visits were not scheduled and no routine SARS-CoV-2 nucleic acid testing was done. No serious adverse events were reported up to day 118 in phase 2 participants.

No new solicited or unsolicited adverse events that occurred between days 42 and 104 in phase 1 participants were considered to be related to the vaccine by the investigators. Additionally, no new serious adverse events were reported. One case of symptomatic COVID-19 was reported in the Algel-only control group. This participant received the first dose on July 17, 2020, but was considered to be lost to follow-up before the second dose was administered. The participant visited the site on Nov 27, 2020, with complaints of chronic anosmia and a history of a positive SARS-CoV-2 rapid antigen test on Aug 16, 2020.

Discussion

In this report, we present interim findings from the phase 2 clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. The overall participant retention rates were 97% in the 3 µg with Algel-IMDG group and 93% in the 6 µg with Algel-IMDG group. Neutralising antibody titres were similar to a panel of convalescent serum samples. All elicited cytokine responses to BBV152 were biased to Th1 cells. The vaccine was well tolerated in both groups with no serious adverse events. Long-term follow-up of phase 1 trial participants showed that neutralising antibody titres persisted, and T-cell memory responses were more pronounced in the 6 µg with Algel-IMDG group compared with pre-vaccination samples.

The most common adverse event in the phase 2 trial was pain at the injection site, followed by headache, fatigue, and fever. No severe or life-threatening (ie, grade 4 and 5) solicited adverse events were reported. No

significant differences in safety were observed between the two groups. However, the study was not powered to compare such differences. After either dose, the combined incidence of local and systemic adverse events in this study is lower than that of other SARS-CoV-2 vaccine platform candidates,[13–16] and similar to that of other inactivated SARS-CoV-2 vaccine candidates.[17,18] However, other vaccine studies have enrolled different populations and have employed varying approaches to measure adverse events.

BBV152 induced antibody binding (to spike glycoprotein and nucleocapsid protein epitopes) and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates.[17,18] Studies have reported the variable persistence of humoral and cell-mediated responses acquired from natural infection.[19,20] In the phase 1 trial of BBV152, we evaluated an accelerated schedule, in which the two doses were administered 2 weeks apart. At day 104 (3 months after the second dose), we observed detectable humoral and cell-mediated responses to SARS-CoV-2. Serum neutralising antibodies were detected in all phase 1 participants at day 104, and the levels of these antibodies were similar to the panel of convalescent serum samples. These findings are in accordance with those of the mRNA-1273 (Moderna) vaccine, which has received emergency use authorisation.[2,21] A sizeable T-cell memory population was also observed at this timepoint. A routine schedule, in which the two doses are administered 4 weeks apart, was evaluated in the phase 2 trial of 3 µg with Algel-IMDG and 6 µg with Algel-IMDG. We found that immune responses (MNT_{50}) were significantly higher with the routine schedule (phase 2) than with the accelerated schedule (phase 1), which is consistent with other reports.[5,22]

BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine adjuvanted with Algel-IMDG. An imidazoquinoline molecule (IMDG), which is a TLR7/8 agonist, has been used to augment cell-mediated responses.[23,24] Both 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations induced responses that were biased to a Th1 phenotype, with IgG1/IgG4 ratios greater than 1. The ratio of Th1/Th2 cytokines was clearly biased to a Th1 response, with increased IFNγ generation.

In the present study, BBV152 induced T-cell memory responses, which was shown by an increased frequency of antigen-specific $CD4^+$ T cells expressing the memory phenotype marker $CD45RO^+$. The increase in the $CD4^+CD45RO^+CD27^+$ T-cell population also indicates the activation of the co-stimulatory marker CD27, and confirms the antigen recall memory T-cell response.[25] Further, the effector function of these cells was supported by the Th1 cytokine secretion observed in ex vivo responses after stimulation of PBMCs for 3 days.[26] These results further corroborate our phase 1 results showing an increased frequency of $CD4^+$ T cells producing IFNγ in participants who received Algel-IMDG-containing formulations. Samples from participants in the Algel-only control group also showed a T-cell memory response, which corroborates a recent study published in 2020 indicating the presence of cross-reactive T-cells in individuals unexposed to SARS-CoV-2.[27] Additionally, two participants in the Algel-only group showed high neutralising antibody titres and IL-6 levels at day 104 of the phase 1 study. In the phase 1 trial, the ability to secrete anti-spike glycoprotein IgG antibodies at day 104 further shows the long-lasting T-cell memory response generated by BBV152. Similar findings supporting long-term

	Dose 1		Dose 2	
	3 µg with Algel-IMDG (n=190)	6 µg with Algel-IMDG (n=190)	3 µg with Algel-IMDG (n=190)	6 µg with Algel-IMDG (n=190)
Local reactions				
Pain at injection site				
Mild	5 (3%)	6 (3%)	7 (4%)	4 (2%)
Moderate	1 (1%)	0	0	1 (1%)
Redness at injection site				
Mild	1 (1%)	1 (1%)	0	0
Moderate	0	0	0	0
Itching				
Mild	1 (1%)	1 (1%)	0	2 (1%)
Moderate	0	0	0	0
Stiffness in upper arm				
Mild	1 (1%)	0	0	0
Moderate	0	0	0	0
Weakness in injection arm				
Mild	0	0	1 (1%)	0
Moderate	0	0	0	0
Systemic reactions				
Body ache				
Mild	0	2 (1%)	1 (1%)	2 (1%)
Moderate	0	1 (1%)	0	0
Fever				
Mild	2 (1%)	5 (3%)	5 (3%)	4 (2%)
Moderate	1 (1%)	3 (2%)	0	0
Headache				
Mild	2 (1%)	1 (1%)	1 (1%)	2 (1%)
Moderate	0	0	0	1 (1%)
Malaise				
Mild	4 (2%)	1 (1%)	3 (2%)	0
Moderate	0	0	0	0
Weakness				
Mild	0	0	1 (1%)	2 (1%)
Moderate	0	1 (1%)	0	0
Rashes				
Mild	0	0	1 (1%)	0
Moderate	0	0	..	0

Data are n (%). The safety analysis set includes all participants who received one dose of the vaccine (n=380). The number of participants who had a solicited adverse event after receiving dose 1 (days 0–7) and dose 2 (days 28–35) is shown.

Table 3: **Mild and moderate solicited adverse events in the safety analysis set**

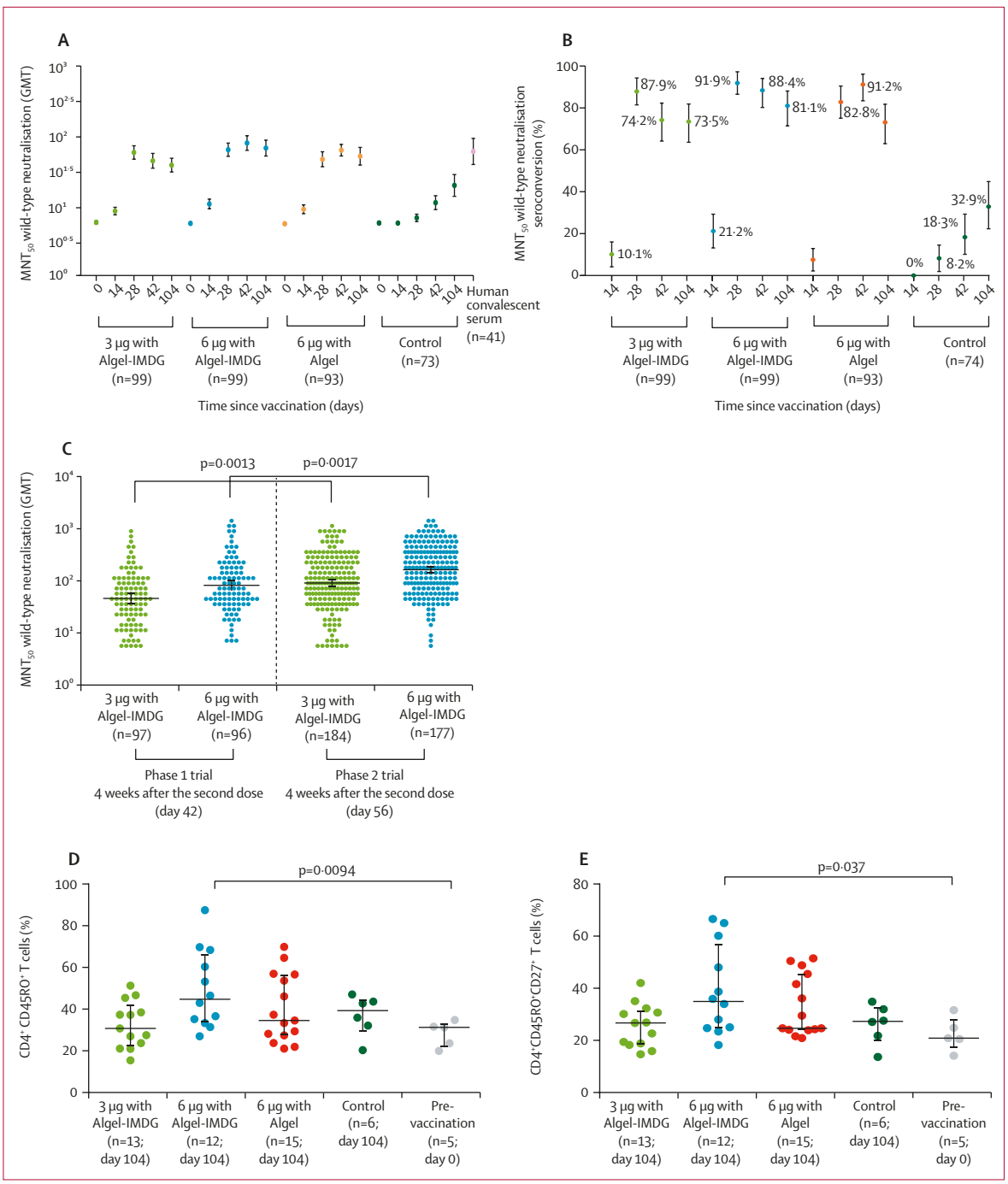

Figure 4: **SARS-CoV-2 wild-type MNT_{50} GMTs (A) and seroconversion rates (B) in phase 1 participants, SARS-CoV-2 wild-type MNT_{50} GMTs in phase 1 and phase 2 participants at 4 weeks after the second vaccination (C), and the proportion of $CD4^+CD45RO^+$ (D) and $CD4^+CD45RO^+CD27^+$ (E) T cells at day 104 in phase 1 participants**
In the phase 1 trial, the dosing schedule was day 0 for the first dose of the vaccine and day 14 for the second dose. In the phase 2 trial, the dosing schedule was day 0 for the first dose of the vaccine and day 28 for the second dose. In A, results at baseline (day 0), 2 weeks after the second vaccination (day 28), 4 weeks after the second vaccination (day 42), and 3 months after the second vaccination (day 104) for the 3 µg and 6 µg with Algel-IMDG groups, the 6 µg with Algel group, and the Algel-only control group in the phase 1 trial are shown. The human convalescent serum panel included specimens from participants with PCR-confirmed symptomatic and asymptomatic COVID-19 obtained at least at least 30 days after diagnosis (41 samples). In B, seroconversion rates were defined by the proportion of post-vaccination titres that were at least four-fold higher than baseline. In D and E, the frequencies of antigen-specific T-cell memory responses at 3 months after the second dose (day 104) in all groups from the phase 1 trial are shown; dots are individual datapoints, and horizontal bars are medians with error bars for IQRs. GMT=geometric mean titre. MNT50=microneutralisation assay.

immunity were reported by Sekine and colleagues[28] in convalescent patients who had previously had COVID-19. Memory B-cell responses from BBV152 are currently being evaluated. Thus far, cell-mediated responses after receipt of other SARS-CoV-2 inactivated vaccine candidates have been minimally reported.

This study was done at a time when the number of daily diagnosed COVID-19 cases was increasing rapidly. In the Algel-only control group (phase 1 trial), seroconversion was reported in six (8·2% [95% CI 1·9–14·5]) of 73 participants at day 28, 13 (18·8% [10·8–30·4]) of 69 participants at day 42, and 23 (33·3% [22·7–45·8]) of 69 participants at day 104. These results suggest that both phase 1 and 2 trials are being done during a period of high ongoing SARS-CoV-2 circulation. Since substantial SARS-CoV-2 PCR positivity was observed in the general population during the study period, in the event of natural exposure to SARS-CoV-2, it is possible that post-vaccination antibody titres in vaccinated participants could be slightly inflated. No cases of COVID-19 were reported in either group of the phase 2 trial, whereas one case of symptomatic COVID-19 was reported in the Algel-only control group of the phase 1 trial. However, illness visits were not scheduled, and routine SARS-CoV-2 nucleic acid testing was not done.

The results reported in this study do not permit efficacy assessments. The evaluation of safety outcomes requires extensive phase 3 clinical trials. We were unable to assess other immune responses (ie, binding antibody and cell-mediated responses) in convalescent serum samples due to the low quantity. Furthermore, no additional data on the age of the participant or the severity of disease from symptomatic individuals were obtained. Comparisons between phase 1 and 2 trials were not done in a randomised set of participants, and no adjustments on baseline parameters were made. Conclusions are to be considered as post-hoc analyses. Even though direct comparisons between the phase 1 and 2 trials cannot be made, the reactogenicity assessments reported in this study were substantially better in the phase 2 trial than the phase 1 trial and other trials with a placebo group.[9] Additionally, the proportion of participants reporting adverse events in the phase 2 trial were lower than in the phase 1 trial. The study coordinators had verified all source documents to ensure that no data were missing or that errors had occurred. Further corroboration with phase 3 safety results is required. This study enrolled a small number of participants aged 12–18 years and 55–65 years. Follow-on studies are required to establish immunogenicity in children and in those aged 65 years and older. Withdrawals in the 6 µg with Algel-IMDG group were higher than the 3 µg with Algel-IMDG group but were not associated with adverse events. Lastly, this study population lacked ethnic, racial, and gender diversity, further underscoring the importance of evaluating BBV152 in other populations. Longitudinal follow-up of additional post-vaccination visits (at months 3, 6, and 12) is important for understanding the durability of immune responses, and is ongoing.

This study has several strengths. To ensure generalisability of the results, this study included participants from diverse geographic locations, enrolling 380 participants across nine hospitals across nine states in India. Based on follow-up data from the phase 1 trial, despite a marginal expected decline in neutralising antibody titres at day 104, BBV152 has shown the potential to provide durable humoral and cell-mediated immune responses. With several reports questioning the efficacy of SARS-CoV-2 vaccines against antigenically divergent strains, we previously reported neutralising antibody responses in homologous and heterologous strain assessments.[9] Day 56 serum samples from 38 participants in the 6 µg with Algel-IMDG group of the phase 2 trial effectively neutralised a SARS-CoV-2 variant of concern (lineage B.1.1.7 or 20B/501Y. V1).[29] On the basis of superior cell-mediated responses in the phase 1 trial, the 6 µg with Algel-IMDG formulation was selected for the phase 3 efficacy trial, which involves 25 800 volunteers and is currently underway (NCT04641481). BBV152 (COVAXIN) has received emergency use authorisation in India.

Contributors

All authors met the criteria for authorship set forth by the International Committee for Medical Editors. HJ, DD, DR, UP, BG, PY, and GS did the immunogenicity experiments. The contract research organisation (Sclin Soft Technologies) was responsible for analysing the data and generating the report. KMV, SRe, VS, SPr, and RE contributed to the manuscript preparation. SRe was the study coordinator and helped immensely with designing the protocol and generating the interim report. PA, SPr, NG, and BB from the Indian Council of Medical Research contributed to the writing of this paper. KE was responsible for overall supervision of the project and review of the final paper. All principal investigators (PR, SV, SKR, CS, SVR, CSG, JSK, SM, VR, and RG) were involved in the scientific review of this paper. All authors and the contract research organisation had full access to masked data in the study and all authors had final responsibility for the decision to submit for publication.

Declaration of interests

RE, HJ, BG, KMV, SRe, DD, DR, UP, SPr, and VS are employees of Bharat Biotech, with no stock options or incentives. KE is the Chairman and Managing Director of Bharat Biotech. PY, GS, PA, NG, SPa, and BB are employees of the Indian Council of Medical Research. PR, SV, SKR, CS, SVR, CSG, JSK, SM, VR, and RG were principal investigators representing the study sites.

Data sharing

The study protocol is provided in appendix 2. De-identified, individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after the approval of a proposal, data can be shared through a secure online platform.

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Phase-III COVAXIN Publication

From : dra@bharatbiotech.com Tue, Jul 06, 2021 09:07 PM

Subject : Phase-III COVAXIN Publication 1 attachment

To : Dr. V.G. Somani DCGI <dci@nic.in>, Vaccine Divsion CDSCO <vaccine-bio@cdsco.nic.in>

Cc : ramarao2488@bharatbiotech.com

Dear Sir/Madam,

Please find the attached Notification of COVAXIN Phase-III Publication for your kind perusal.

Thanks & Regards,
Regulatory Affairs,
Ph: 040-4645 4537.
Mobile: 8886619761

Phase III publication with Annexure.pdf
952 KB

Annexure Sheet

(To be filled up by the firm)

1. Application Ref No. : BBIL/RA/21/451
   - Application Date : 06/07/2021
2. Name of the Company : Bharat Biotech Int. Ltd.
   - Address of the Company : Genome Valley, Shameerpet, Telangana
3. Subject: Notification of COVAXIN phase III publication
4. Challan Fees/No./Date : _____
5. Basic Division _____
   (New Drugs, / Import Division / Biological (Vaccine, Stem Cell, Blood Products, recombinant products) / Medical Devices / Diagnostic Kits / Blood Bank / Cosmetics / Narcotic Drug / Export & Neutral Codes / Test license / LVP Division Pharmacovigilance)
6. Type of Application Miscellaneous (Choose the type from the list given in page/2).

I ~~Mr./~~ Dr. / ~~Mrs~~ Krishna Mohan
representing M/s Bharat Biotech International Ltd.

Hereby solemnly affirm that the information furnished as above are absolutely true and is based on the facts.

Signature & Seal

BHARAT BIOTECH INTERNATIONAL LIMITED
BHARAT BIOTECH
Hyderabad, TS, India

Type of Application

• Investigational New Drug (IND) • New Drug Approval (NDA) • Subsequent New Drug Application (SNDA) • Post Marketing Surveillance Study (PMS) • Periodic Safety update Reports (PSUR) • Package insert approval • Clinical Trial Approval (Domestic) (CTA) • Global Clinical Trial (GCT) • Post Approval Change • BE Study (Domestic approval) (BED) • BE Study for Export (BEE) • Serious Adverse Events (SAE) • Registration Certificate (RC) • Import License (Form-10) (IL) • Import of Drugs having Dual Use • Request for Shelf Life Extension • Drug Manufacturing License (DML) (CLAA) • NOC for Form-29 (Trial Batch release)	• Test License (Form-11) (TL) • Export NOCs • Neutral Code • Narcotic Drugs • Correspondences relating to Blood Banks Licensing (BBL) • Cosmetics • WHO-GMP/COPP • Permission under Rule -37 • Free Sale Certificate • Miscellaneous Correspondence N.B. Submission made in response to query or for an amendment to permission issued should be accompanied with a copy of query or permission letter.

BHARAT BIOTECH
Lead Innovation

Ref No: BBIL/RA/21/451 06.07.2021

To
The Drugs Controller General (India),
Ministry of Health and Family Welfare,
Government of India,
FDA Bhawan, Kotla Road,
New Delhi.

Sub: To notify COVAXIN Phase 3 trial manuscript titled '**Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial'.**

Dear Sir/Madam,

We hereby notify the panel with our phase 3 trial publication titled '**Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial'** submitted to LANCET on 02 July 2021.

Please find the manuscript allied.

Thank you!

Sincerely,

Dr. V. Krishna Mohan,
Whole-Time Director (BBIL)

Enclosure:
1. Manuscript

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Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial

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ABSTRACT:

Background:

We report the clinical efficacy against COVID-19 infection of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine formulated with a Toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG).

Methods:

We did a double-blind, randomised, multicentre, phase 3 clinical trial in 25 Indian hospitals to evaluate the efficacy, safety, and immunological lot consistency of BBV152. Healthy adults (age 18–98 years) randomised 1:1 using a computer-generated randomisation scheme received two intramuscular doses of vaccine or placebo administered four weeks apart. The primary outcome was laboratory-confirmed symptomatic COVID-19, occurring at least 14 days after the second dose. Secondary outcomes were efficacy in sub-groups for age (18–< 60 years and ≥ 60 years) and in participants with pre-existing stable medical conditions. We also evaluated safety, reactogenicity, and consistency of immune responses for three consecutive manufacturing lots.

Findings:

Between November 16, 2020 and January 7, 2021 we recruited 25,798 participants who were randomised to BBV152 or placebo groups; 24,419 received two doses of BBV152 (n = 12,221) or placebo (n = 12,198). In a case-driven analysis, 130 cases of symptomatic COVID-19 were reported in 16,973 (0·77%) participants with follow-up at least two weeks after the second vaccination; 24 occurred in the vaccine group and 106 in placebo recipients giving an overall vaccine efficacy of 77·8% (95% CI: 65·2–86·4). Sixteen cases, one vaccinee and 15 placebo recipients, met the severe symptomatic COVID-19 case definition giving a vaccine efficacy of 93·4% (57·1–99·8). Efficacy against asymptomatic COVID-19 was 63·6% (29·0–82·4). BBV152 conferred 65·2% (95% CI: 33·1–83·0) protection against

the SARS-CoV-2 Variant of Concern, B.1.617.2 (Delta). BBV152 was well tolerated with no clinically or statistically significant differences in the distributions of solicited, unsolicited, or serious adverse events between vaccine and placebo groups. No cases of anaphylaxis or vaccine-related deaths were reported.

Interpretation:

BBV152 was immunogenic and highly efficacious against symptomatic and asymptomatic COVID-19 variant associated disease, particularly against severe disease in adults. Vaccination was well tolerated with an overall incidence of adverse events observed over a median of 146 days that was lower than that observed with other COVID-19 vaccines.

Funding:

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Clinicaltrials.gov: NCT04641481

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human coronavirus, has spread globally causing the COVID-19 pandemic [1]. Vaccines from multiple manufacturers are needed to address the global demand for SARS-CoV-2 vaccines as there is currently insufficient supply. Furthermore, the widely publicised mRNA-based and viral vector vaccines that have been shown to be effective themselves introduce cold chain hurdles and vaccine wastage making them difficult to adopt for many countries.

Bharat Biotech has developed BBV152, a COVID-19 vaccine based on the whole-virion SARS-CoV-2 vaccine strain NIV-2020-770 inactivated with ß-propiolactone. Preclinical studies in rodents and nonhuman primates (NHP) have demonstrated appropriate tolerability, immune responses and protective efficacy [2–4]. We previously reported interim findings from phase 1 and 2 controlled, randomised, double-blind trials on the safety, reactogenicity and immunogenicity of different formulations, which resulted in the selection of a formulation containing a 6 µg dose formulated with a Toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) for further clinical development [5,6]. In use, BBV152 is stored between 2°C and 8°C, which will ease immunisation cold chain requirements. Here, we report findings from a phase 3 case-driven efficacy study including a sub-set analysis of efficacy against newly identified variants of SARS-CoV-2. We also present a nested controlled, randomised, double-blind trial on the safety and immunogenicity of the selected BBV152 formulation, including comparisons of immune responses to three consecutive manufacturing lots measured at day 56, one month after the second dose.

METHODS

Study Design and Participants

We assessed the efficacy, safety and immunogenicity of two intramuscular 6 µg Algel-IMDG doses of BBV152 in a randomised, blinded, placebo-controlled, multi-centre study done in 25 centres in India. The trial was approved by the National Regulatory Authority (India) and the respective Ethics Committees of each study centre and was conducted in compliance with all International Conference for Harmonization (ICH) Good Clinical Practice guidelines. The trial was registered on clinicaltrials.gov: NCT04641481.

Participants were adult volunteers 18 years of age or older who were healthy or had stable chronic medical conditions. Volunteers were screened for eligibility based on their health status, including their medical history, vital signs, and physical examination results. Eligible participants provided signed and dated informed consent forms at enrolment. Key exclusion criteria included any diagnosis with an immunocompromising condition, or treatment with immunosuppressive therapy. Detailed inclusion and exclusion criteria can be found in the Protocol (*Supplementary appendix 2)*. A minimum of 20% of the entire sample size was to be comprised of "at-risk participants" defined as being either over 60 years of age, having a coexisting comorbidity (cardio-vascular, diabetes, or any other chronic stable condition), or having a BMI $\geq$ 35 kg/m^2. A maximum of 5% of the total enrolled participants were selected from members of the healthcare community.

The primary study objective was to assess the efficacy of the study vaccine in preventing PCR-confirmed symptomatic COVID-19 in a case-driven manner, together with sub-group analyses of asymptomatic efficacy and symptomatic efficacy according to age (18–59 and $\geq$ 60 years of age), and any chronic stable, medical condition. Major secondary objectives were assessments of the safety and immunogenicity of BBV152 in sub-groups of participants.

Randomisation and masking

Unblinded statisticians (Cytespace Research and Octalsoft) were involved in designing the randomisation plan and the interactive web response system (IWRS) system for the study. The randomisation plan, stratified for the presence or absence of chronic conditions, was used to generate treatment allocation. The master randomisation list, containing the randomisation number and intended treatment allocation, as well as the kit code, was sent to the IWRS and kits were despatched to the sites according to the IWRS by an unblinded statistician from the CRO tasked with labelling of vaccine vials and the generation of the master randomisation code. Participants were assigned a computer-generated randomisation code and each vial was labelled with a unique code that ensured appropriate masking. The IWRS system assigned the same treatment group for the second visit. Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to the treatment group allocation, and masked study nurses at each site were responsible for vaccine preparation and administration.

Procedures

BBV152 (Bharat Biotech, Hyderabad, India) is a whole-virion ß-propiolactone-inactivated SARS-CoV-2 vaccine. The vaccine strain NIV-2020-770 contains the D614G mutation, which is characterised by an aspartic acid to glycine shift at amino acid position 614 of the spike protein [7]. Each 0.5 mL dose contains 6 µg of virus antigen formulated with Algel-IMDG, an imidazoquinoline class molecule that is a Toll-like receptor (TLR) 7/8 agonist (IMDG) adsorbed to Algel. Placebo vials contained the Algel formulation alone without IMDG or inactivated virus antigen. Vaccine and placebo were supplied and stored in a single-use glass vials at 2°C to 8°C, with no on-site dose preparation necessary. The appearance, colour, and viscosity were identical for vaccine and placebo.

At the screening/vaccination visit (visit 1), participants were evaluated with both SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (PCR) (ICMR-NIV 2019 nCOV Assay Kit V 3.1) and serology tests (Merilisa, ICMR-NIV Anti-SARS CoV-2 Human IgG ELISA COVID KAVACH), before each injection (*Supplementary materials, pages 5–6)*. Regardless of the outcome of these tests, participants were randomly allocated using the IWRS in a 1:1 ratio to receive two doses of vaccine or placebo on days 0 and 28. Participants who were subsequently found to have a positive PCR test were excluded from receiving the second dose. All females had a urine pregnancy test.

Participants were monitored for 2 hours after vaccination for any acute reactions. No prophylactic medication (ibuprofen/acetaminophen) was prescribed either before or after vaccination. Participants were instructed to record local and systemic reactions daily for seven days after each vaccination (days 0 to 7 and days 28 to 35) using a paper-based memory aid which solicited local and systemic adverse events. Solicited local adverse events included pain at the injection site and swelling, and systemic adverse events included fever, fatigue/malaise, myalgia, body aches, headache, nausea/vomiting, anorexia, chills, generalised rash, and diarrhoea. The memory aid contained fields for symptom onset, severity, time to resolution, and concomitant medications and was collected during the subsequent visit to the site. Routine telephone calls were scheduled following the first seven days after each vaccination. Participants reported all unsolicited adverse events and serious adverse events throughout the study. Adverse events were graded according to severity (mild, moderate, or severe) and by relationship (related or unrelated) to the investigational vaccine, as detailed in the protocol.

Study sites were classified into three categories: Category 1: in addition to administering the vaccine or placebo, a series of post-dose follow-up telephone calls (every two weeks) were scheduled to detect suspected symptomatic COVID-19 (n = 16,477) and those who met

symptomatic criteria had a clinical assessment (*Protocol, Supplementary appendix 2*), and a nasopharyngeal swab (NP) was taken for PCR confirmation. Category 2: in addition to symptomatic follow-up, a series of post-dose 2 NP swabs were collected on-site for detection of asymptomatic COVID-19 infection at monthly intervals (n = 8,721); Category 3: in addition to follow-up for symptomatic and asymptomatic COVID-19 infection, blood samples were collected for immunological assessments (n = 600). Unscheduled illness visits were encouraged for participants till day 360 (± 14 days). All participants were instructed to contact the team on an as-needed basis.

Outcomes

The primary outcome was the efficacy of the BBV152 vaccine in preventing a first occurrence of symptomatic COVID-19 (any severity) with onset at least 14 days after the second dose in the per-protocol population composed of participants who were SARS-CoV-2 negative by PCR and serology at baseline, had no major protocol deviations, and followed-up for at least two weeks after the second dose. End points were judged by an independent adjudication committee masked to treatment allocation. COVID-19 cases were defined as participants with at least two of the following symptoms: fever (temperature ≥ 38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one SARS-CoV-2 PCR-positive nasopharyngeal swab. COVID-19 cases were followed daily to assess symptom severity until symptoms resolved. In PCR-positive participants who consented, an additional NP swab for genotyping and a blood sample for evaluating correlates of protection were collected. Secondary efficacy outcomes included efficacy in subgroups defined by age (18–59 years and ≥ 60 years), gender, and health risk for severe disease (presence or absence of a coexisting chronic medical condition), efficacy against variants of concern, and efficacy against asymptomatic

infections occurring after receipt of two doses of vaccine/placebo periodically at a month's interval in 8,721 participants, among whom 6,289 participants were SARS-CoV-2 negative at baseline and included in the per protocol analysis.

The immunological secondary outcome was evaluation of consistency of immune responses from three consecutive manufacturing lots. This was based on geometric titres (GMTs) evaluated using a wild-type virus microneutralisation assay (MNT_{50}) (*Supplementary materials, page 8*). Immune responses against three SARS-CoV-2 epitopes, the S1 protein and the receptor binding domain (RBD) of the spike protein, and the nucleocapsid antigen (N-antigen) were measured as IgG responses by ELISA (*Supplementary materials, page 9*). All sera were analysed in a blinded manner at Bharat Biotech (Hyderabad, India) and submitted to the CRO for data analysis and preparation of the report. Safety secondary outcomes were the proportions of participants with solicited local and systemic reactogenicity within seven days after vaccination, and with unsolicited adverse events recorded within 28 days after vaccination.

Statistical Analysis

The study was designed to obtain a two-sided 95% CI for vaccine efficacy with lower bound $\geq 30\%$. Based on a true efficacy of 60% and power of 85%, the case-driven trial was planned to accrue 130 cases. Assuming 1% incidence of PCR-confirmed symptomatic COVID-19 disease among placebo recipients during follow-up beginning 14 days after the second dose, the number of participants required to accrue 130 cases was approximately 18,572. To allow for a 20% baseline seropositivity rate or PCR-confirmed COVID-19 and 10% loss to follow-up, we planned to enrol 25,800 participants. Sample size estimation was performed using PASS 13 software (NCSS, Kaysville, Utah, USA).

Estimation of vaccine efficacy was based on person-time incidence rates: VE = 1 – (nv/Fv) / (np/Fp) = 1 – R, where R = (nv/Fv) / (np/Fp); nv and np are the numbers of participants who develop PCR-confirmed symptomatic COVID-19 among BBV152 vaccine and placebo recipients, respectively, and Fv and Fp are the corresponding total lengths of follow-up in years in the two groups, with follow-up in years defined as follow-up in days divided by 365.25. We also define the parameter P, the proportion of participants with COVID-19 who were in the vaccine group. Then a two-sided confidence interval (CI) around the estimated VE is obtained by converting an exact CI for the probability parameter P, using the observed Fp/Fv, to a CI for VE. Interim analyses were planned at 43 and 87 primary endpoint cases, using an O'Brien-like Lan-DeMets alpha spending function [8].

Safety endpoints are reported as number and % of participants. Immunological endpoints are expressed as GMTs with 95% confidence intervals (CIs) calculated from 95% CIs for means of $\log_{10}$ (titre), which used t-distributions. The criterion for consistency (equivalence) (equivalence) of the immune response to BBV152 across three consecutive manufacturing batches was that two-sided 95% CIs for the ratio of GMTs for all pairs of lots be entirely contained within the interval [0.5, 2.0], limits which have frequently been used for the related concept of non-inferiority in vaccine trials [9].

For continuous variables (less than 20 observations), medians and IQRs are reported. Exact binomial calculations were used for the CI estimation of proportions. Wilson's score test was used to test differences in proportions. A result with two-sided $P \leq 0.05$ or one-sided $P \leq 0.025$, as appropriate, was considered statistically significant. This report contains results regarding immunogenicity and safety outcomes (captured on days 0 to 56) and efficacy results with a median of 99 days (two weeks after a second dose). Certain prespecified subgroup analyses are not included in this report but will be presented in future analyses

when a larger dataset is available. Descriptive and inferential statistics were performed using SAS 9·4.

Role of the Funding Source

Bharat Biotech and the Indian Council of Medical Research (ICMR) were responsible for the funding the study, designing the protocol, and writing this manuscript. The funder of the study had no role in data collection or data analysis. However, the funder provided technical guidance on deriving methodologies for data analysis. A CRO (IQVIA) was responsible for overall conduct and data analysis. Masked laboratory assessments were done at Bharat Biotech, and masked datasheets were sent to the CRO for decoding and analysis. The unmasked randomisation list was not shared with the study sponsor. An independent data and safety monitoring board (DSMB) periodically reviewed unblinded efficacy and unblinded safety data.

RESULTS

Between November 16, 2020 and Jan 7, 2021, we screened 26,028 volunteers and recruited and vaccinated 25,798 participants across 25 sites (**Figure 1**). At the data cut-off date of May 17, 2021, a total of 23,803 (92·3%) participants had a median of 146 days of safety data available after the first dose. Among these participants, 7058 (27·5%) had at least one coexisting condition. The mean age was 40·1 years, and 10·7% of participants were older than 60 years of age. A large proportion of participants were seropositive at baseline (30%) and were thus excluded from the per-protocol analysis but contributed to the safety dataset. All baseline characteristics were similar between vaccine and placebo groups (**Table 1**).

Efficacy

Among the 16,973 participants in the per protocol analysis population (*Supplementary table 2, page 10*), the planned efficacy analysis occurred after the accrual of 130 symptomatic

COVID-19 cases which started to present soon after the beginning of the observation period (**Figure 2**). There were 24 (0·28%) cases among 8471 participants in the vaccine arm and 106 (1·25%) cases among 8502 participants in the placebo group, resulting in estimated vaccine efficacy of 77·8% (95% CI: 65·2–86·4). There were sixteen cases who met the severe symptomatic COVID-19 cases definition, all but one of whom were in the placebo group, resulting in a vaccine efficacy of 93·4% (95% CI: 57·1–99·8). Efficacy against asymptomatic COVID-19 infections was 63·6% (29·0–82·4). In the 1858 elderly participants in the analysis, the split of cases between vaccine and placebo groups was 5 (0·56%) of 893 participants and 16 (1·66%) of 965, respectively, giving an efficacy of 67·8% (8·0–90·0). Efficacy in the 15,115 participants who were younger than 60 years was 79·4% (66·0–88·2) (**Table 2**).

Immune Responses

At day 56 in the groups who received lots 1, 2, 3 or placebo GMTs (MNT_{50}) of SARS-CoV-2 neutralising antibodies were 130·3 (95% CI: 105·8–160·4), 121·2 (97·6–150·5), 125·4 (101·3–155·1), and 13·7 (10·7–17·4), respectively (**Table 4**). GMT ratios between all three pairs of lots were consistently similar: lots 1:2 GMT ratio 1·08 (95% CI: 0·80–1·45), lots 1:3 GMT ratio 1·04 (0·77–1·40), and lots 2:3 GMT ratio 0·97 (0·71–1·31). All the 95% CIs for the GMT ratios were contained within the interval [0·50, 2·0] (*Supplementary figure 1, page 11*), meeting the predefined criterion for a consistent immune response across lots.

There were no marked differences in GMTs for neutralizing antibodies at Day 56 when assessed based on age or gender (*Supplementary table 3, page 12*). The GMT was higher (194.3 [95% CI: 134.4–280.9, n = 48] in vaccinees who were seropositive for SARS-CoV-2 IgG at baseline than in those who were seronegative (118.0 [104.0–134.0]).

At Day 56 IgG titres to all three epitopes (S1 protein, RBD, and N protein) were detected after two doses. For all three lots combined the GMTs at Day 56 were 9742 EU/mL (95% CI: 8949–10606) for S1 protein, 4124 EU/mL (3731–4557) for RBD-competitive binding, and 4161 EU/mL (3736–4633) for SARS-CoV-2 N protein assays (**Table 4**). The placebo group did not display any meaningful change in titres over the course of the study for any of the immune targets.

Safety

There were 15 deaths in the study, none of which were considered by the investigators to be related to the vaccine or placebo; six deaths were reported to be related to COVID-19. In BBV152 recipients there were five deaths all due to causes unrelated to vaccination: cerebellar haemorrhage, haemorrhagic stroke, ovarian cancer with metasases, sudden cardiac death, and COVID-19. Ten placebo recipients died, also from unrelated conditions: alcohol overdose, myocardial infarction, cardiac arrest with underlying hypertension, five from COVID 19 and two which remain to be determined. No anaphylactic events were reported.

The vaccine had a good reactogenicity profile with similar rates of solicited, unsolicited, and serious adverse events and adverse events of special interest in vaccine and placebo groups. Serious adverse events occurred in 99 participants; 39 (0·30%) received BBV152 and 60 (0·47%) received placebo (*Supplementary Table 4, page 13*). Two related serious adverse events were reported among BBV152 recipients. Long-term safety monitoring will continue for 1 year after administration of the first dose of BBV152.

Solicited adverse events analyses are provided for all enrolled 25,798 participants (*Supplementary table 5, page 14*). Overall, incidence rates were lower after the second dose than the first, and tended to be slightly higher in the BBV152 group than the placebo group. However, all incidence rates were low, with only 12·4% reporting any solicited AE after

vaccine or placebo. Among the local or systemic solicited AEs, only local injection pain was reported with an incidence greater than 1% (*Supplementary table 4, page 13*). Similar proportions of vaccine (3·04%) and placebo (2·78%) groups reported local pain after the first dose, falling to 1·81% and 1·62% after the second dose, respectively. Other local AEs were reported by less than 0.3% of participants in any group after either dose. Solicited systemic AE were reported less frequently, after 2·57% and 1·92% of first doses of vaccine or placebo, respectively. The most frequent solicited systemic AE overall was headache, followed by pyrexia, fatigue and myalgia but at incidences below 1% in both groups. Rates of local and systemic AEs reported in the BBV152 group as mild (11·2%), moderate (0·8%), or severe (0·3%) were comparable to the placebo group (mild [10·8%], moderate [1·1%], and severe [0·4%]). Unsolicited AEs were reported by 1·8% and 1·7% of vaccinees and placebo recipients, respectively. No significant differences were observed between the vaccine and placebo groups, the P value for all comparisons being > 0·05.

DISCUSSION

We report findings from the phase 3 efficacy, safety and immunogenicity clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. In the final per-protocol analysis, measured 14 days after the second of two doses of BBV152, there was a vaccine efficacy of 77·8% (95% CI: 65·2–86·4) against symptomatic COVID-19 disease, and perhaps more importantly a higher efficacy against severe COVID-19 of 93·4% (57·1–99·8). Thus, cases of severe disease which require hospitalisation and have threatened to overwhelm healthcare facilities will be markedly decreased in fully vaccinated populations Although the study was not powered to definitively assess efficacy in subgroups with different ages, gender, or the presence of pre-existing comorbid conditions, efficacy rates for symptomatic COVID-19 were all high in these sub-groups (>66%) with the lower limits of the respective 95% CIs being above 30% in all cases except for the > 60 years group.

This phase 3 study confirms our earlier observations on the safety and immunogenicity profiles of BBV152 in phase 1 and 2 trials [5,6]. There were no safety concerns raised, no reports of anaphylactic events after BBV152 administration, and all adverse events (solicited, unsolicited, and serious adverse events) were well balanced between BBV152 and placebo groups. One possibly related serious adverse event in the BBV152 group was a case of immune thrombocytic purpura that occurred 39 days after the second dose in a participant who was SARS-CoV-2 seropositive at baseline, which resolved in four days. After any dose, the combined incidence rate of local and systemic adverse events in this study is noticeably better than the rates for other SARS-CoV-2 vaccine platform candidates [10,11], and comparable to the rates for other inactivated SARS-CoV-2 vaccine candidates [12].

When measured as neutralising antibodies, the three consecutive manufacturing lots of vaccine induced consistent humoral immune responses, and when measured as ELISA IgG responses against three SARS-CoV-2 epitopes (S1 and RBD of the spike protein, and the nucleocapsid antigen) antibody titres were similar across all lots (**Table 4**). Further, BBV152 generated comparable neutralising immune responses in participants < 60 and ≥ 60 years of age (*Supplementary table 3, page 12)*; vaccine efficacy was 79·4 % (95% CI: 66·0–88·2) and 67·8% (8·0–90·0) in the younger and older subgroups, respectively (**Table 2**).

The recent surge in SARS-CoV-2 variant strains has raised concerns regarding the efficacy of vaccines against the new Variants of Concern (VoC). Some COVID-19 vaccines, notably Coranavac and ChAdOx1, have been reported to have diminished efficacy against the Gamma (P1) and Beta (B.1.351) variants first isolated in Brazil and South Africa [11,13]. The ChAdOx1 vaccine is reported to have equivalent efficacy against the Alpha (B.1.1.7) variant, which is widely circulating [14]. Effectiveness after two doses of the mRNA-based vaccine, BNT162b2, decreased from 93·4% (95% CI: 90·4–95·5) against B.1.1.7 to 87·9% (78·2–93·2) against B.1.617.2 [15]. With ChAdOx1 effectiveness after two doses decreased

from 66.1% (54.0–75.0) against B.1.1.7 to 59.8% (28.9–77.3) against B.1.617.2 [15]. The emergence of VoC occurred during the conduct of our trial, and we obtained additional consent to collect additional NP swabs from RT-PCR-confirmed symptomatic COVID-19 participants. All sequences were generated by the National Institute of Virology, Pune, India using the quantitative approach [16,17]. Controls were checked to ensure no evidence of amplification in the negative tests and that expected RNA quantification was consistent with cycle threshold (Ct) values provided by the testing laboratories. All samples were processed by laboratory staff masked to vaccine allocation. A total of 79 variants were reported from 16,973 samples, 18 in the vaccine and 61 in the placebo group. Among 50 Delta (B.1.617.2) positive-confirmed cases, 13 and 37 participants were in the vaccine and placebo arms, resulting in vaccine efficacy of 65·2% (95% CI: 33·1–83·0). In breakthrough symptomatic Delta variant infections, based on Ct values, the viral load in the vaccine arm was significantly lower than the placebo arm. Efficacy against the Kappa (B.1.617.1) variant was 90·1% (95% CI: 30·4–99·8). No cases of severe variant-related cases of COVID-19 were reported in the vaccinees but four severe cases were reported in the placebo recipients infected with Alpha, Kappa, Delta, and unclassified variants respectively (Table 3). As previously reported BBV152-induced antibodies show no significant decrease in neutralisation activity against the Alpha (B.1.1.7) variant, but demonstrate marginal reductions in neutralisation activity, by 2-, 2-, 3-, and 2.7-fold, respectively, of the B.1.1.28, B.1.617.1, B.1.351 (Gamma), and B.1.617.2 (Delta) variants [18–21].

No licensed SARS-CoV-2 vaccine has reported efficacy against asymptomatic infection in a randomised controlled trial, based on nucleic acid testing, although the mRNA vaccine, BNT162b2, has been associated with decreased asymptomatic SARS-CoV-2 infections in healthcare workers [22]. Several other vaccine studies employed surrogate markers to assess asymptomatic efficacy by periodically collecting serum from trial participants and assessing

for anti-SARS-CoV-2-nucelocapsid binding antibody (N antigen) [10]. In this study, a total of 8,721 participants made monthly clinical visits for routine medical check-ups and collection of NP swabs for PCR confirmation of asymptomatic COVID-19. In the per protocol set, 3,248 and 3,041 participants in BBV152 and placebo groups, respectively, were enrolled and as per the cut-off date, up to two months after the second dose, 14 and 33 positive PCR confirmations have been reported in the vaccine and placebo groups, respectively, an efficacy of 66·6 % (95% CI: 23·7–80·4). A study with the ChAdOx1 vaccine found no efficacy (3·8%) against asymptomatic infections, albeit direct comparisons cannot be made as a surrogate serological marker was used [10]. Our findings corroborate well with preclinical protective efficacy studies in hamsters and NHP, which reported lower and upper airway protection against SARS-CoV-2 infection [3,4].

This study has several limitations. Due to the low number of cases reported between doses 1 and 2, we cannot calculate vaccine efficacy after a single dose. This report contains a median safety follow-up of 146 days for all participants, so long-term safety follow-up of BBV152 is required and is currently underway. The data presented on efficacy against variants other than Delta must be considered preliminary as the numbers reported are small. Additional efforts to assess the clinical efficacy of BBV152 against VoC are being planned. The potential establishment of a correlate of protection is not feasible at the time of this report. Finally, this study population lacked ethnic and racial diversity, underscoring the importance of evaluating the efficacy of BBV152 in other populations.

Although the study was designed to vaccinate and follow participants for one year after the second dose, given the nature of the pandemic in India and the emergency use authorization for BBV152, after meeting the pre-defined efficacy success criteria, the DSMB and sponsor decided to unblind those placebo participants who were eligible to receive an approved COVID-19 vaccine. Unblinding in such cohorts was planned only after the accrual of the

protocol pre-specified 130 cases, in a phased manner: health care professionals, individuals ≥45 years, followed by those <45 years. Our sample estimations accounted for 20% seropositivity. As we observed baseline seropositivity rates of 30% and due to the unblinding of the health care professionals and elderly individuals (who are eligible for COVID-19 vaccination), the protocol was amended to expand the sample size to 30,800, with 5,000 additional participants now being enrolled in Brazil. This will ensure the study evaluates the efficacy of BBV152 against VoC and provides an opportunity to accrue additional severe COVID-19 cases as well as more racial diversity. This manuscript contains data from the Indian cohort only.

However, this study does have several strengths. The study enrolled participants with ages ranging from 18 to 98 years and found no major differences in immune responses across the broad age groups of under- and over-60 year-olds. Participants considered to be at-risk of acquiring COVID-19 were prioritised, so a total of 2,750 participants were above 60 years of age and 7,065 reported at least one pre-existing medical condition across ages. To ensure generalisability, this study was conducted with participants from diverse geographic locations, enrolling 25,798 participants across 25 hospitals. This is the first trial to report preliminary promising findings on the efficacy against asymptomatic infections and clinical lot-to-lot immunological comparability.

The most common solicited adverse event was pain at the injection site, followed by headache, fatigue, and fever. No severe or life-threatening (Grade 4 and 5) solicited adverse events were reported. Although the study was not powered to find such differences, no meaningful safety differences were observed between the groups. After any dose, the combined incidence rate of local and systemic adverse events in this study is noticeably better than the rates for other SARS-CoV-2 vaccine platform candidates [23–27] and comparable to the rates for other inactivated SARS-CoV-2 vaccine candidates [28,29].

However, other vaccine studies enrolled different populations and employed varying approaches to measure adverse events.

The positive safety, immunogenicity and efficacy results presented here will support regulatory submissions for emergency use authorisation (EUA) which BBV152 (COVAXIN™) has already received in 23 countries. With the inclusion of Vaccine Vial Monitor 7, storage at 2°C–8°C, and a 28-day open-vial policy (limiting open-vial vaccine wastage by 10–25%), the established efficacy of BBV152 against symptomatic and asymptomatic infection will be critical towards mitigating the COVID-19 pandemic.

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Author Contributions

All authors met the criteria for authorship set forth by the International Committee for Medical Editors. RE contributed to the manuscript preparation and KMV, SPr, KE, WB, NG,

SPa, PA, and BB reviewed the manuscript. RE and KMV and were responsible for overall project coordination. SRe, VS, and VA were led clinical operations and helped immensely with designing the protocol. WB was involved with the study design and statistical analysis plan. VP, PY, and GS led the virological confirmation and genomic sequencing efforts. The contract research organisation (IQVIA) was responsible for analysing the data and generating the report. All principal investigators (SK, SR, PRe, SV, CS, SR, SM, AP, PRa, RG, MM, SM, PB, and LK) were involved in the scientific review of this paper. RE, KMV, PY, GS, VA, and VS had full access and verified the masked data in the study, and can vouch for its accuracy and completeness. All authors had final responsibility for the decision to submit for publication.

Competing Interests

This work was funded by Bharat Biotech International Limited and co-funded by the Indian Council of Medical Research. RE, KMV, SPr, SRe, VA and VS are employees of Bharat Biotech, with no stock options or incentives. Co-author, KE, is the Chairman and Managing Director of Bharat Biotech. WB is an independent statistical development consultant. VP, PY, GS, PA, NG, and BB are employees of The Indian Council of Medical Research. SK, SR, PRe, SV, CS, SR, SM, AP, PRa, RG, MM, SM, PB, and LK were principal investigators representing the study sites.

Data Sharing Statement

The study protocol is provided as *Supplementary Appendix 2*. Individual participant (de-identified) data will be made available when the trial is complete upon direct request to the corresponding author with an appropriate research proposal. Once such a proposal is approved data will be shared through a secure online platform.

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Table 1: Demographic of participants in the safety population

Parameter	BBV152 n (%)	Placebo n (%)
N =	12,879	12,874
Age, years		
(Mean ± SD)	40·1 ± 13·8	40·1 ± 14·1
Range	18, 92	19, 97
Sex, n (%)		
Female	4214 (32·7)	4254 (33·0)
Male	8665 (67·3)	8620 (66·9)
Body Mass Index (BMI), kg/m^2		
	24·3 ± 4·4	24·3 ± 4·3
Pre-existing medical conditions, n (%)		
Stable cardiovascular disease	557 (4·3)	523 (4·1)
Stable respiratory disease	126 (1·0)	170 (1·3)
Controlled diabetes	706 (5·5)	735 (5·7)
Stable liver disease	25 (0·2)	28 (0·2)
Severe obesity (BMI > 35)	56 (0·4)	94 (0·7)
Other stable co-morbidities	839 (6·5)	910 (7·1)
Multiple risk categories	458 (3·6)	497 (3·9)
Baseline assessments for SARS-CoV-2 positivity*		
Positive for anti-SARS-CoV-2 IgG	3932 (30·5)	3886 (30·2)
Positive for SARS-CoV-2 by PCR	108 (0·8)	105 (0·8)

* At the screening or initial vaccination visit (visit 1) participants were evaluated for exposure to SARS-CoV-2 with both anti-SARS-CoV-2 IgG by ELISA and reverse-transcriptase polymerase chain reaction (PCR). Regardless of the outcome of these tests, participants were randomised and allocated to a group.

572 **Table 2:** Efficacy against SARS-CoV-2 after at least 14 days following a second dose of BBV152 vaccine in the per protocol population.

Efficacy Endpoint	Total cases n/N (%)	BBV152 n/N (%)	Placebo n/N (%)	Vaccine efficacy (CI)*
Symptomatic COVID-19	130/16973 (0·77)	24/8471 (0·28)	106/8502 (1·25)	77·8 (65·2–86·4)
Severe Symptomatic COVID-19	16/16973 (0·09)	1/8471 (0·01)	15/8505 (0·18)	93·4 (57·1–99·8)
Symptomatic COVID-19 in participants 18–59 years	109/15115 (0·72)	19/7578 (0·25)	90/7537 (1·19)	79·4 (66·0–88·2)
Symptomatic COVID-19 in participants ≥ 60 years	21/1858 (1·13)	5/893 (0·56)	16/965 (1·66)	67·8 (8·0–90·0)
Symptomatic COVID-19 in participants with a pre-existing medical condition	49/4846 (1·01)	12/2328 (0·52)	37/2518 (1·47)	66·2 (33·8–84·0)
Asymptomatic COVID-19	47/6289 (0·73)	13/3248 (0·40)	33/3041 (1·09)	63·6 (29·0–82·4)
Symptomatic and asymptomatic COVID-19	75/6289 (1·19)	19/3248 (0·58)	56/3041 (1·84)	68·8 (46·7–82·5)

573 * 95.006% CI used for primary analysis of symptomatic COVID-19 to adjust for interim analyses, 95% CI otherwise. Primary efficacy was based on the
574 per protocol population, including randomly assigned participants who were seronegative at baseline and received two doses of either vaccine or placebo,
575 and remained on study at least 14 days after their second dose with no previous virologically-confirmed SARS-CoV-2 infection. COVID-19 cases were
576 defined as occurring in participants who had at least two of the following symptoms: fever (temperature ≥ 38°C), chills, myalgia, headache, sore throat, or
577 a new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or
578 clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab that was PCR positive for SARS-CoV-2.
579

Table 3: Efficacy against variants of interest (VoI) and concern (VoC).

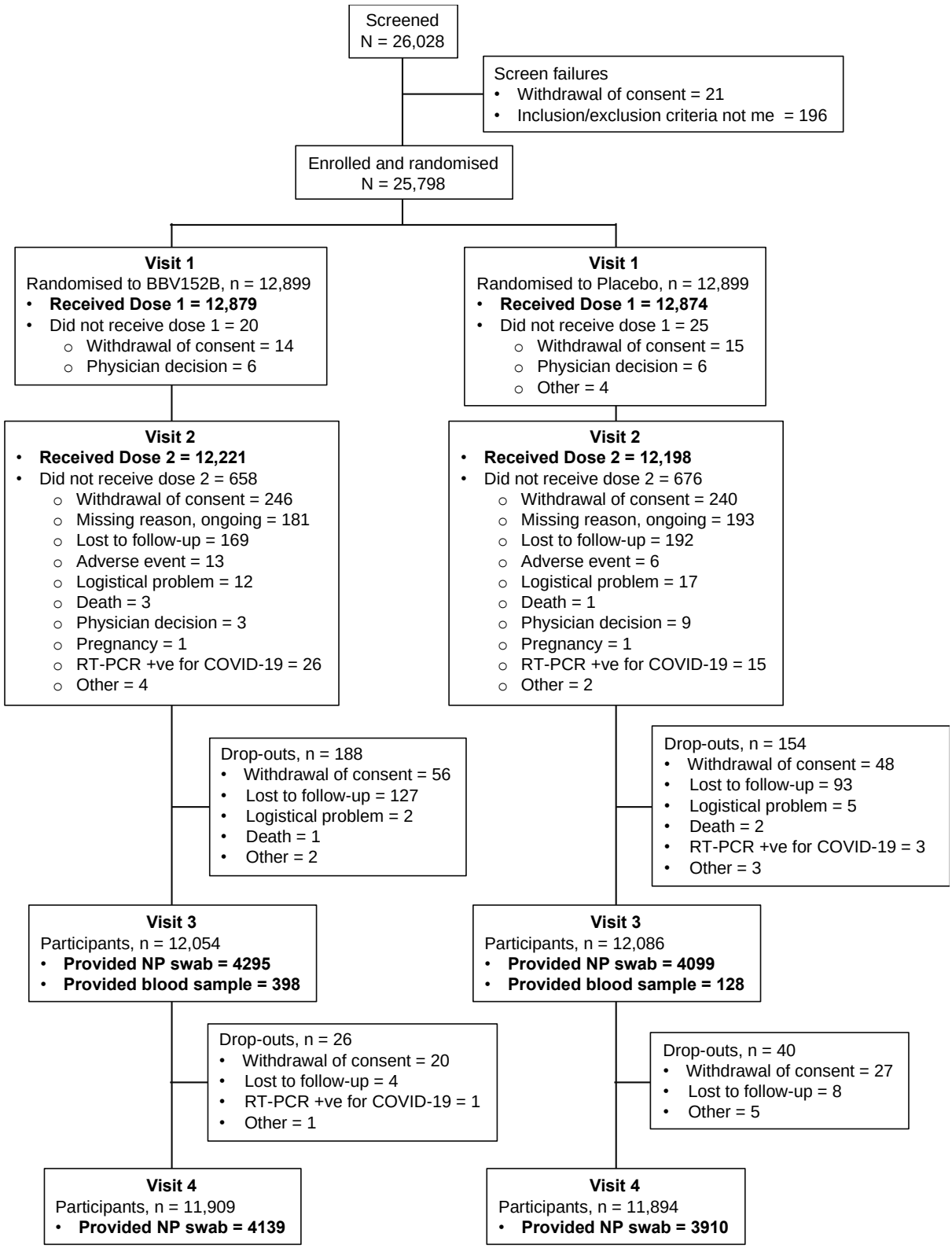
Variants (VoC/VoI)	**Total number of cases** n/N (%)	**BBV152** n/N (%)	**Placebo** n/N (%)	**Vaccine efficacy (CI)***
All variant related COVID-19	79/16,973 (0·47)	18/8471 (0·21)	61/8502 (0·72)	70·8 (50·0–83·8)
B.1.617.2 (Delta)	50/16,973 (0·29)	13/8471 (0·15)	37/8502 (0·44)	65·2 (33·1–83·0)
B.1.617.1 (Kappa)	11/16,973 (0·06)	1/8471 (0·01)	10/8502 (0·12)	90·1 (30·4–99·8)
B.1.1.7 (Alpha)	4/16,973 (0·02)	1/8471 (0·01)	3/8502 (0·04)	--
Other	14/16,973 (0·08)	3/8471 (0·04)	11/8502 (0·13)	73·0 (-2·2–95·2)
All variant related severe COVID-19	4/16,973 (0·02)	0/8471 (0)	4/8502 (0·04)	--
Ct values	**All cases**	**BBV152** Mean	**Placebo** Mean	**Mean difference of BBV152 – Placebo [95% CI])**
B.1.617.2 (Delta) – E gene	20·11	25·55	18·20	1·42 (1·28–1·57)
B.1.617.2 (Delta) - ORF gene	22·97	28·29	21·09	1·35 (1·24–1·46)
All variants – E gene	20·44	24·01	19·38	1·24 (1·14–1·36)
All variants - ORF gene	23·26	26·55	22·29	1·19 (1·10–1·28)

Data include per protocol population only. In those participants who met the definition for symptomatic COVID-19 and were PCR positive an additional nasopharyngeal swab for genotyping was collected. No viable sequence obtained or unprocessed due to cycle threshold (Ct) >30. Other pangolin lineages detected include D614G (n = 7), B.1.36 (n = 3), B.1.1.419 (n = 1), B. 1.153 (n = 1), B. 1. 351 and B.1.618 (n = 1 each in placebo), and A (n = 1). The > 1 lower bound of 95% CI for mean ratio indicates a statistical significance; in breakthrough symptomatic Delta variant infections the viral load in the vaccine arm was significantly lower than the placebo arm. We failed to retrieve the complete genome from 6 swab samples (all in placebo) subjected to sequencing.

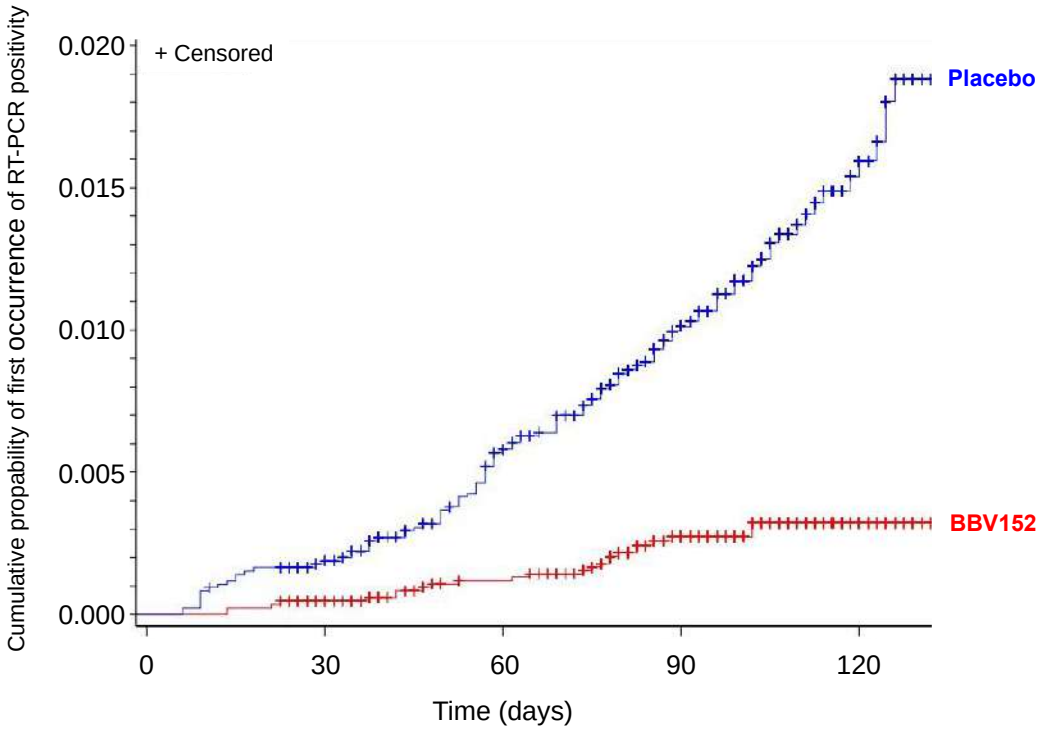
Table 4: SARS-CoV-2 neutralising (MNT_{50}) and binding antibody responses (Anti-S1 protein, RBD-binding, and N protein IgG). Data are shown for neutralising response expressed as MNT_{50} at Days 0 (baseline) and Day 56, four weeks after the second vaccination. Day 56 IgG antibody titres are expressed as arbitrary ELISA units, all baseline titres being at the cut-off for the assay (reciprocal of 1:500 dilution).

Assay		**Geometric mean titres** (95% CI) **at Day 56 in sub-sets of the different study groups**				
		BBV152				**Placebo**
		Lot 1	Lot 2	Lot 3	All lots	
SARS-CoV-2 MNT_{50}	N =	132	129	136	397	125
	Day 0	**9·9** (8·3, 11·9)	**8·6** (7·5, 9·9)	**7·9** (7·0, 8·9)	**8·8** (8·0, 9·6)	**8·9** (7·7, 10·4)
	N =	128	125	133	386	119
	Day 56	**130·3** (105·8, 160·4)	**121·2** (97·6, 150·5)	**125·4** (101·3, 155·1)	**125·6** (111·2, 141·8)	**13·7** (10·7, 170·4)
S-protein binding IgG	N =	129	124	134	387	121
	Day 56	**9760** (8483, 11228)	**10404** (8873, 12198)	**9152** (7912, 10586)	**9742** (8949, 10606)	**1528** (1323, 1765)
RBD-binding IgG	N =	129	124	134	387	121
	Day 56	**4266** (3584, 5079)	**4423** (3669, 5333)	**3740** (3180, 4399)	**4124** (3731, 4557)	**1443** (1261, 1651)
N protein binding IgG	N =	129	124	134	387	121
	Day 56	**4551** (3800, 5450)	**4183** (3423, 5111)	**3798** (3165, 4558)	**4161** (3736, 4633)	**1485** (1275, 1730)

Figure 1: CONSORT Flow Diagram



595 **Figure 2:** Kaplan Meier plot of first occurrence of virologically confirmed (RT-PCR positive)
596 symptomatic cases of COVID-19 (per-protocol set)



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Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial

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Summary

Background To mitigate the effects of COVID-19, a vaccine is urgently needed. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) or alum (Algel).

Methods We did a double-blind, multicentre, randomised, controlled phase 1 trial to assess the safety and immunogenicity of BBV152 at 11 hospitals across India. Healthy adults aged 18–55 years who were deemed healthy by the investigator were eligible. Individuals with positive SARS-CoV-2 nucleic acid and/or serology tests were excluded. Participants were randomly assigned to receive either one of three vaccine formulations (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) or an Algel only control vaccine group. Block randomisation was done with a web response platform. Participants and investigators were masked to treatment group allocation. Two intramuscular doses of vaccines were administered on day 0 (the day of randomisation) and day 14. Primary outcomes were solicited local and systemic reactogenicity events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. Secondary outcome was seroconversion (at least four-fold increase from baseline) based on wild-type virus neutralisation. Cell-mediated responses were evaluated by intracellular staining and ELISpot. The trial is registered at ClinicalTrials.gov (NCT04471519).

Findings Between July 13 and 30, 2020, 827 participants were screened, of whom 375 were enrolled. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only). After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10·5–26·1) participants in the 3 µg with Algel-IMDG group, 21 (21%; 13·8–30·5) in the 6 µg with Algel-IMDG group, 14 (14%; 8·1–22·7) in the 6 µg with Algel group, and ten (10%; 6·9–23·6) in the Algel-only group. The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (nine [2%]), and nausea or vomiting (seven [2%]). All solicited adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose. One serious adverse event of viral pneumonitis was reported in the 6 µg with Algel group, unrelated to the vaccine. Seroconversion rates (%) were 87·9, 91·9, and 82·8 in the 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, and 6 µg with Algel groups, respectively. $CD4^+$ and $CD8^+$ T-cell responses were detected in a subset of 16 participants from both Algel-IMDG groups.

Interpretation BBV152 led to tolerable safety outcomes and enhanced immune responses. Both Algel-IMDG formulations were selected for phase 2 immunogenicity trials. Further efficacy trials are warranted.

Funding Bharat Biotech International.

Introduction

Spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has led to a global COVID-19 pandemic. Vaccines from multiple manufacturers will be needed to address the global need for SARS-CoV-2 vaccines and thus far, 194 vaccine candidates are in development.[1]

A desirable characteristic for any COVID-19 vaccine candidate is the ability to induce T-helper-1 cell (Th1) responses.[2] Whole-virion inactivated vaccines are usually formulated with Alum, which does not have the ability to induce cell-mediated responses.[3,4] An imidazoquinoline molecule, which is a toll-like receptor (TLR) 7/8 agonist, has been used to stimulate cell-mediated responses.[5,6] Algel-IMDG (an imidazoquinoline molecule chemisorbed on alum [Algel]) has been designed to traffic vaccine antigen directly to draining lymph nodes without diffusing into the systemic circulation. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine adjuvanted with Algel-IMDG.

Preclinical studies in mice, rats, and rabbits showed appropriate safety profiles and humoral and cell-mediated responses.[7] Two live viral challenge protective efficacy studies in hamsters and non-human primates were done.

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For the **WHO COVID-19 dashboard** see https://covid19.who.int/

Research in context

Evidence before this study

We searched PubMed on Jan 15, 2020, for published research articles using the search terms "SARS-CoV-2", "COVID-19", "vaccine", and "clinical trial", with no language or date restrictions. We found several publications on COVID-19 vaccine clinical trials from mRNA, adenovirus, protein subunit, and inactivated vaccines.

As of Jan 15, 2020, nine vaccines have received emergency use authorisation to be administered to prevent COVID-19. Inactivated vaccines have been approved for decades with well established safety profiles. Immune responses from two other inactivated vaccines have been reported; however, with few results on cell-mediated responses. Bharat Biotech has developed a vero cell-based whole-virion inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine (BBV152) formulated with alum and a TLR7/8 agonist producing a T-helper-1 cell skewed response. This vaccine candidate reported protection in two live viral non-human primate and hamster challenge models.

Added value of this study

We report the preliminary analyses for the safety and immunogenicity of the vaccine candidate BBV152 in 375 vaccinated adults. All vaccine groups had similar reactogenicity and serological outcomes to the control group. BBV152 led to enhanced immune responses; the 3-µg and 6-µg Algel-IMDG vaccines induced T-cell responses that were biased to T-helper-1 cells.

Implications of all the available evidence

Findings from other inactivated SARS-CoV-2 vaccine candidates are corroborating. However, to the best of our knowledge, ours is the only reported inactivated COVID-19 vaccine candidate inducing cell-mediated responses and humoral neutralising responses. Both Algel-IMDG formulations will be assessed in a phase 2 immunogenicity trial.

In both studies, protection was evident by rapid clearance of virus in the lower and upper respiratory tract, and absence of lung pathology (after viral challenge).[8,9] Here, we report the interim findings from the randomised, controlled, double-blind phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 and one control group containing Algel (without antigen). This phase 1 trial was done with the intention of selecting two formulations for progression to the phase 2 trial.

Methods

Study design and participants

This is a randomised, double-blind, multicentre, phase 1 trial to assess the safety, reactogenicity, tolerability, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine (BBV152) in healthy adult volunteers, at 11 hospitals across nine states of India (appendix pp 5, 13). Participants were aged 18–55 years and deemed healthy by the investigator at the time of enrolment. At the screening visit, participants were tested with both SARS-CoV-2 nucleic acid (TRUPCR SARS-CoV-2 RT-PCR; 3B BlackBio Biotech, Bhopal, India) and serology (chemiluminescence immunoassay; LIAISON SARS-CoV-2 S1/S2 IgG; DiaSorin, Saluggia, Italy) tests (conducted at Dr Dangs Lab [New Delhi, India] using commercially available assays; appendix p 3). If found positive for any one test, they were excluded from the trial. The median time between the screening visit and vaccination visit was 4 days (range 3–6). Other key exclusion criteria were an axillary temperature of more than 37·0°C and known allergy to any vaccine component. Participants were screened for eligibility on the basis of their health status, including their medical history, laboratory findings (haematology, biochemistry, and urine tests), vital signs, and physical examination results, and were enrolled after providing signed and dated informed consent forms. Full inclusion and exclusion criteria are in the protocol.

See Online for appendix

The trial was approved by the National Regulatory Authority (India) and the respective ethics committees and was conducted in compliance with all International Council for Harmonization Good Clinical Practice guidelines.

Randomisation and masking

The master randomisation list was uploaded on the interactive web response system, which contained the randomisation number and intended allocation. The depot manager uploaded the kit code list and assigned the kits to the sites that had the kit codes and the allocation groups. At the site level, the system would set the randomisation number and the allotment of the kit without displaying the true group allocation, and the system would allocate the same treatment group for the second visit. For the first 50 participants, a block size of five with ten blocks was generated for the 3 µg with Algel-IMDG and control groups at a ratio of 4:1. In the remaining participants, the number of blocks was 20. For the first 15 blocks, a block size of 16 was used to randomly assign participants (3:5:5:3) to 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, 6 µg with Algel, or Algel-only control. The next five blocks were size 17, and used to randomly assign participants (3:5:5:4) to 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, 6 µg with Algel, or Algel-only control. An unmasked contract research organisation, Sclin Soft Technologies, generated the randomisation list for the study.

Participants, investigators, study coordinators, study-related personnel, and the funder were masked to treatment group allocation (excluding an unmasked member of the contract research organisation, who was

tasked with the dispatch and labelling of vaccine vials and the generation of the master randomisation code). Participants were assigned a computer-generated randomisation code that maintained masking. The masked study nurse was responsible for vaccine preparation and administration. Each vial contained a unique code that ensured appropriate masking. The appearance, colour, and viscosity were identical across all vaccine and control formulations.

Procedures

The virus strain (NIV-2020-770) containing the Asp614Gly mutation, isolated from a COVID-19 patient and sequenced at the Indian Council of Medical Research National Institute of Virology, was provided to Bharat Biotech.[10] Biosafety level 3 manufacturing facilities and a well established Vero cell manufacturing platform (with proven safety in other licensed live and inactivated vaccines) were used for the rapid development of BBV152.[11–16]

BBV152 (manufactured by Bharat Biotech) is a whole-virion β-propiolactone-inactivated SARS-CoV-2 vaccine. The NIV-2020-770 strain contains the Asp614Gly mutation, which is characterised by aspartic acid to glycine shift at the amino acid position 614 of the spike protein.[10]

The candidates were formulated with two adjuvants: Algel (alum) and Algel-IMDG, an imidazoquinoline class molecule (TLR7 and TLR8 agonist) adsorbed onto Algel. After their eligibility was established, participants were assigned to the four groups. The control group contained only a sterile phosphate-buffered solution and Algel. Both the vaccine and control were stored at 2–8°C.

The vaccine (BBV152) and the control were provided as a sterile liquid that was injected intramuscularly (deltoid muscle) at a volume of 0·5 mL/dose in a two-dose regimen on day 0 (day of randomisation) and day 14. This accelerated schedule was chosen given the context of the ongoing pandemic. No onsite dose preparation was required. Each glass vial contained a single dose of either vaccine or control formulation that required no additional dilution steps. No prophylactic medication (ibuprofen or acetaminophen) was prescribed either before or after vaccination.

The follow-up visits were scheduled on days 7, 28, 42, 104, and 194 after vaccination. The study was done in a dose-escalation manner after completing vaccination in the first 50 participants with 3 μg with Algel-IMDG (the lowest antigen concentration) and the control; these participants were monitored for 7 days for safety. The independent data safety monitoring board reviewed masked safety data and decided whether the trial was allowed to continue with enrolment of the remaining participants into all groups.

Outcomes

The primary outcome was the number and proportion of participants with solicited local and systemic reactogenicity events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. The secondary outcomes was immunogenicity, in terms of geometric mean titres (GMTs) and four-fold seroconversion rate of neutralising antibodies, from baseline to days 14, 28, 42, 104, and 194.

Safety assessments

The unsolicited adverse events were recorded for 28 days after vaccination. Laboratory values (serum chemistry, haematology, and urine) were compared before vaccination (day 0) and after vaccination (day 28).

Participants were observed for 2 h after vaccination to assess reactogenicity. They were instructed to record local and systemic reactions within 7 days (days 0–7 and days 14–21) after vaccination using a diary card. The diary card contained fields for symptom onset, severity, time to resolution, concomitant medication, and was collected during the next visit to the site. Routine telephone calls were scheduled after the first 7 days after each vaccination.

Solicited local adverse events were pain at the injection site and swelling, and systemic adverse events, including fever, fatigue or malaise, myalgia, body aches, headaches, nausea or vomiting, anorexia, chills, generalised rash, and diarrhoea. All unsolicited adverse events were reported by participants throughout the study. Adverse events were graded according to the severity score (mild, moderate, or severe) and whether they were related or not related to the investigational vaccine, as detailed in the protocol (appendix p 6).

Immunogenicity assessments

IgG responses against the spike (S1) glycoprotein, receptor-binding domain, and nucleocapsid protein of SARS-CoV-2 were assessed by an in-house-developed ELISA and are expressed as GMTs. Neutralising antibody titres were assessed by wild-type virus neutralisation assays: a microneutralisation assay (MNT_{50}) and a plaque-reduction neutralisation test ($PRNT_{50}$), at Bharat Biotech. These assays were based on the Asp614Gly strain (appendix p 4). To establish interlaboratory comparability, a subset of randomly selected serum samples (n=50) was analysed by MNT_{50} at the National Institute of Virology. Additionally, three laboratory strains were used in vitro for $PRNT_{50}$ at the National Institute of Virology: the BBV152 strain NIV-2020-770 homologous, and two heterologous strains from the O clade (nCoV-Q111 and nCoV-Q100). Genomic analyses of strains were reported by Potdar and colleagues.[17] Only the NIV-2020-770 strain contained the Asp614Gly mutation.[10]

To compare vaccine-induced responses to natural SARS-CoV-2 infections, 41 convalescent serum samples (collected within 1–3 months after nucleic acid test-based diagnosis) were tested by MNT_{50}. These serum samples were collected from both self-reported symptomatic (n=25) and asymptomatic (n=16) patients with COVID-19 at Nizam's Institute of Medical Sciences (NIMS;

Hyderabad, India). The age of these participants was 23–62 years. For symptomatic patients, ascertainment of severity grading and requirement of supplemental oxygen was not obtainable. A participant who achieved seroconversion was defined as having a post-vaccination titre at least four-fold greater than their respective pre-vaccination titre. Serum samples were analysed in a masked manner at Bharat Biotech and the National Institute of Virology.

Cell-mediated responses were assessed in a subset of participants at one site (NIMS). The contract research organisation generated a random code containing randomisation numbers, which was provided to the staff to identify participants. Blood (3–5 mL) was collected from those participants who consented to the additional volume on days 0 and 28. Peripheral blood mononuclear cells were collected to assess IFN-γ by ELISpot (13 in vaccinated groups and six in the control group). Intracellular cytokine staining was used to assess T-cell responses in the remaining samples that contained an adequate number of cells. To ensure equal distribution, eight samples in each vaccine group were selected. These assays were done at Indoor Biotechnologies (Bangalore, India) and Bharat Biotech. All samples were analysed in a masked manner. The details of all assay methods are in the appendix (p 5).

Statistical analysis

Using a two-sided 5% significance level, power was calculated for several levels of the absolute difference between seroconversion rates for vaccine formulations, and we decided on the power to find a statistically significant difference between rates if the true underlying absolute difference was at least 20%. The allocation ratio was 1:1:1 for three vaccine formulations and 4:1 for the vaccine (all formulations combined) to placebo. The placebo group was not included in the sample size calculations. For a sample size of 90 for each formulation, the power to find a statistically significant absolute difference for a true underlying difference of 20% was at least 80% if the lower seroconversion rate for two formulations was at least 52%, which is lower than the seroconversion rate we expected for an effective vaccine. The sample size chosen was 100 per vaccine formulation, to allow for loss of data because of withdrawals or loss to follow-up. We did not incorporate an adjustment for multiple comparisons, because this phase 1 study was not a pivotal study for licensure, and we planned to

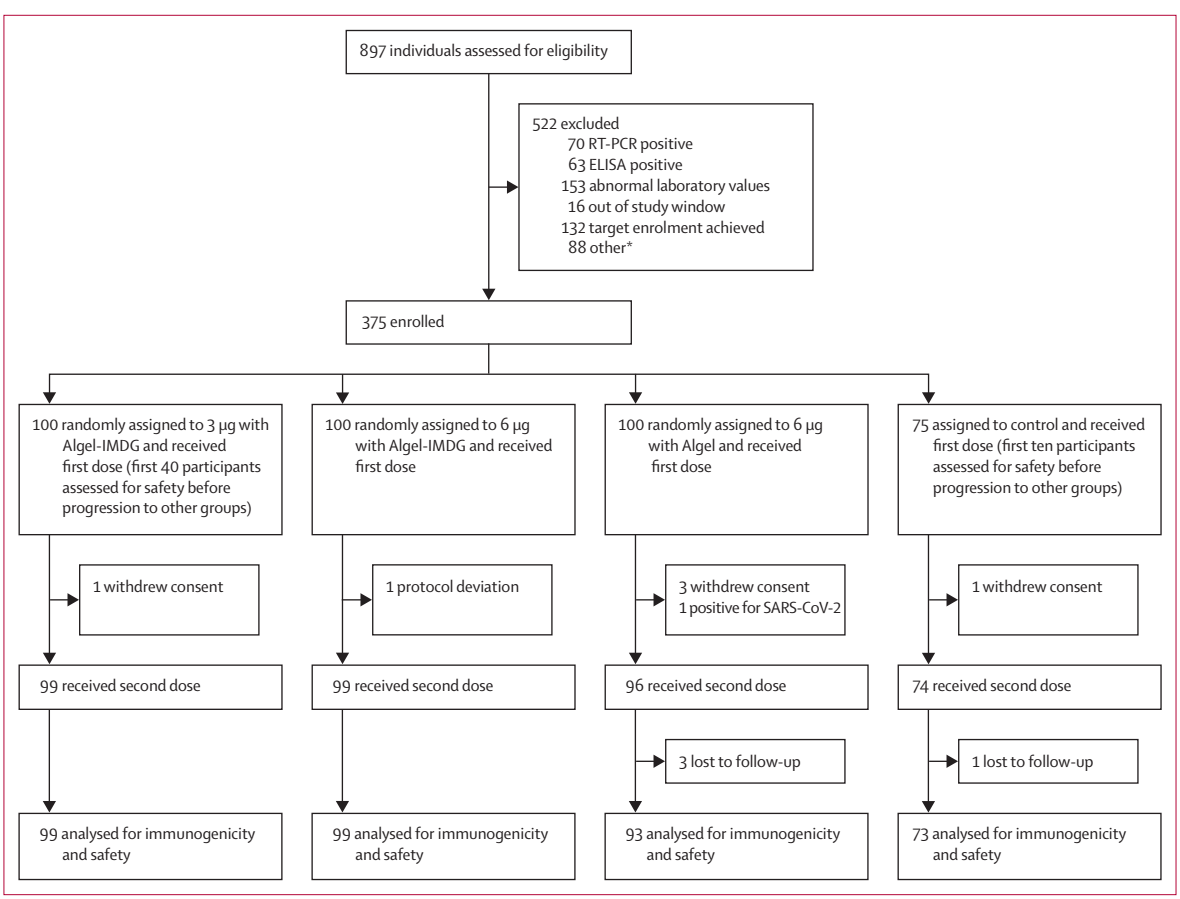

Figure 1: **Trial profile**

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Unable to contact the participant for vaccination or withdrawal of consent.

choose two vaccine formulations from the phase 1 study for further assessment. Sample size estimation was done using PASS 13 software, version 13.0.17.

Safety endpoints are described as frequencies (%). GMTs with 95% CI are used for immunological endpoints. For continuous variables (<20 observations), medians and IQRs are reported. The exact binomial calculation was used for the CI estimation of proportions. The Wilson's test was used to test differences in proportions. CI estimation for the GMT was based on the $\log_{10}$ (titre) and the assumption that the $\log_{10}$ (titre) was normally distributed. A comparison of GMTs was done with *t* tests on the means of the $\log_{10}$ (titre). Significance was set at $p<0{\cdot}05$ (two-sided). This preliminary report contains results regarding immunogenicity (days 0–28) and safety outcomes (days 0–42). Descriptive and inferential statistics were assessed using SAS, version 9.2. The trial was registered at ClinicalTrials.gov (NCT04471519).

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report, but was involved in study design. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 13 and 30, 2020, 897 individuals were screened and 375 were enrolled. Of the 522 initially screened individuals who were excluded, 133 participants were excluded because they were positive for SARS-CoV-2 by nucleic acid test or serology and 153 were excluded because of abnormal laboratory values (figure 1). The first 50 participants enrolled were monitored for 7 days after vaccination, and on the basis of the independent data safety monitoring board review of masked safety data, the trial was allowed to continue with enrolment of the remaining participants into all groups. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only). Demographic characteristics of the participants were similar across groups (table 1).

After dose 1, solicited local adverse reactions were reported by five (5%; 95% CI 1·9–11·8) participants in the 3 µg with Algel-IMDG group, five (5%; 1·9–11·8) in the 6 µg with Algel-IMDG group, one (1%; 0·05–6·2) in the 6 µg with Algel group, and three (3%; 1·04–12·03), in the Algel-only control group. Solicited systemic adverse reactions were reported by five (5%; 1·9–11·8) participants in the 3 µg with Algel-IMDG group, 14 (14%; 8·1–22·7) in the 6 µg with Algel-IMDG group, eight (8%; 3·8–15·6) in the 6 µg with Algel group, and seven (7%; 4·2–18·9) in the Algel-only group (table 2; appendix p 14). The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (nine [2%]), and nausea or vomiting (seven [2%]). All adverse events were mild or moderate in severity and resolved within 24 h of onset. After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10·5–26·1) participants in the 3 µg with Algel-IMDG group, 21 (21%; 13·8–30·5) in the 6 µg with Algel-IMDG group, 14 (14%; 8·1–22·7) in the 6 µg with Algel group, and ten (10%; 6·9–23·6) in the Algel-only group. All adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose than the second. No significant differences were observed between the vaccinated and control groups.

44 unsolicited adverse events were reported by 24 (6%) of 375 participants (appendix p 6). Biochemical, haematological, and urine parameters outside of the normal

	BBV152 3 µg with Algel-IMDG (n=100)	BBV152 6 µg with Algel-IMDG (n=100)	BBV152 6 µg with Algel (n=100)	Algel only (n=75)
Age, years				
Median (IQR)	32·5 (25·0–40·0)	35·0 (25·0–40·0)	32·0 (25·0–40·0)	29·0 (24·0–38·0)
≥18 to ≤25	29 (29%)	28 (28%)	31 (31%)	22 (29%)
≥26 to ≤40	47 (47%)	47 (47%)	45 (45%)	37 (49%)
>40 to ≤55	24 (24%)	25 (25%)	24 (24%)	16 (21%)
Sex				
Men	78 (78%)	82 (82%)	76 (76%)	61 (81%)
Women	22 (22%)	18 (18%)	24 (24%)	14 (19%)
Body-mass index*, kg/m²	24·8 (3·5)	25·8 (4·2)	24·9 (3·7)	24·6 (3·5)
Vital signs				
Systolic blood pressure, mm Hg	122·9 (8·5)	123·5 (7·9)	121·6 (8·3)	123·6 (8·5)
Diastolic blood pressure, mm Hg	79·4 (5·9)	79·3 (6·5)	79·2 (5·3)	79·4 (6·4)
Pulse rate, beats per min	77·4 (7·3)	78·1 (8·2)	78·0 (5·9)	78·3 (7·6)
Respiratory rate, breaths per min	16·9 (2·3)	16·7 (2·6)	17·1 (2·6)	16·9 (2·2)
Temperature, °C	36·6 (0·4)	36·5 (0·6)	36·5 (0·4)	36·6 (0·4)
Sites				
All India Institute of Medical Sciences, New Delhi	3 (3%)	6 (6%)	3 (3%)	4 (5%)
All India Institute of Medical Sciences, Patna	25 (25%)	9 (9%)	6 (6%)	7 (9%)
Gillukar Multispeciality Hospital	10 (10%)	14 (14%)	19 (19%)	12 (16%)
Institute of Medical Sciences and SUM Hospital	4 (4%)	5 (5%)	9 (9%)	5 (7%)
Jeevan Rekha Hospital	1 (1%)	1 (1%)	2 (2%)	0
Nizam's Institute of Medical Sciences	11 (11%)	14 (14%)	15 (15%)	7 (9%)
Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences	22 (22%)	10 (10%)	15 (15%)	16 (21%)
Prakhar Hospital	8 (8%)	10 (10%)	11 (11%)	10 (13%)
Rana Hospital and Trauma Centre	1 (1%)	3 (3%)	2 (2%)	2 (3%)
Redkar Hospital	7 (7%)	14 (14%)	13 (13%)	9 (12%)
SRM Hospital and Research Center	8 (8%)	14 (14%)	5 (5%)	3 (4%)

Data are n (%) or mean (SD) unless otherwise stated. The intention-to-treat population included all participants who received at least one dose. *Calculation was based on the bodyweight and height measured at the time of screening. No data on race were collected; all participants were south Asian.

Table 1: **Demographic characteristics of the participants in the intention-to-treat population**

	Dose 1				Dose 2			
	3 μg with Algel-IMDG (n=100)	6 μg with Algel-IMDG (n=100)	6 μg with Algel (n=100)	Algel only (n=75)	3 μg with Algel-IMDG (n=100)	6 μg with Algel-IMDG (n=100)	6 μg with Algel (n=100)	Algel only (n=75)
Local reactions								
Pain at injection site								
Mild	4 (4%; 1·1–9·9)	4 (4%; 1·1–9·9)	1 (1%; 0·0–5·5)	2 (3%; 0·3–9·3)	2 (2%; 0·2–7·0)	1 (1%; 0·03–5·5)	1 (1%; 0·0–5·5)	0
Moderate	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	0	0	0	0	0
Swelling								
Mild	0	0	0	1 (1%; 0·0–7·2)	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Systemic reactions								
Fever								
Mild	0	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	2 (2%; 0·2–7·0)	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0
Moderate	0	1 (1%; 0·0–5·5)	2 (2%; 0·2–7·0)	0	0	0	0	0
Body ache								
Mild	0	1 (1%; 0·03–5·5)	0	0	0	0	0	0
Moderate	0	1 (1%; 0·0–5·5)	1 (1%; 0·0–5·5)	0	1 (1%; 0·0–5·5)	0	0	0
Fatigue								
Mild	1 (1%; 0·0–5·4)	0	0	0	1 (1%; 0·03–5·4)	0	3 (3%; 0·6–8·5)	0
Moderate	2 (2%; 0·2–7·0)	3 (3%; 0·6–8·5)	0	0	1 (1%; 0·0–5·5)	0	0	0
Headache								
Mild	1 (1%; 0·03–5·5)	2 (2%; 0·2–7·0)	0	5 (7%; 2·2–14·9)	0	0	0	0
Moderate	0	3 (3%; 0·6–8·5)	2 (2%; 0·2–7·0)	0	0	0	0	0
Nausea or vomiting								
Mild	1 (1%; 0·03–5·5)	2 (2%; 0·2–7·0)	2 (2%; 0·2–7·0)	2 (3%; 0·3–9·3)	0	0	0	0
Moderate	0	0	0	0	0	0	0	0

Data are n (%; 95% CI). The safety set includes all participants who received one dose of the vaccine (n=375). Dose 1 events are from days 0–7 and dose 2 events are days 14–21. The grading scale for most adverse events was based on the US Food and Drug Administration (FDA) guidance document for toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. For adverse events where grading was not mentioned in the FDA guidance document, we have used the common terminology criteria for adverse events grading. There were no severe adverse events.

Table 2: **Solicited adverse events in the safety set**

ranges had no corroborating clinical manifestations (appendix pp 7–9).

One serious adverse event was reported in the 6 μg with Algel group. The participant was screened on July 25 and vaccinated on July 30. 5 days later, the participant reported fever and headache (initially reported as a solicited adverse event), and on Aug 8 tested positive for SARS-CoV-2 (by a nucleic acid test). The symptoms were initially mild in nature, with the onset of relapsing fever requiring admission to hospital on Aug 15. The participant had stable vital signs (except body temperature) during their hospital stay and did not require supplemental oxygen. The participant was discharged on Aug 22 after a negative nucleic acid test result. The event was not causally associated with the vaccine. No other symptomatic SARS-CoV-2 infections were reported between days 0 and 75. However, follow-up of routine SARS-CoV-2 nucleic acid testing was not done on any scheduled or illness visit.

IgG titres (GMTs) to all epitopes (spike protein, receptor-binding domain, and nucleocapsid protein) increased rapidly after the administration of both doses (figure 2A–C; appendix pp 3–4). Both 3 μg and 6 μg with Algel-IMDG groups reported similar anti-spike, anti-receptor binding, and anti-nucleoprotein IgG titres (GMTs), adding to the dose-sparing effect of the adjuvant. Binding antibody titres to the whole-virion inactivated antigen are shown in the appendix (p 15). The mean isotyping ratios (IgG1/IgG4) were greater than 1 for all vaccinated groups, which was indicative of a Th1 bias (figure 2D).

Seroconversion rates (after the second dose), based on MNT_{50} were 87·9% (95% CI 79·8–94·3) in the 3 μg with Algel-IMDG group, 91·9% (84·6–96·0) in the 6 μg with Algel-IMDG group, and 82·8% (73·7–89·2) in the 6 μg with Algel group (figure 3A). Seroconversion (at day 28) in the control group was reported in six (8% [3·6–17·2]) of 75 participants, suggestive of asymptomatic infection. The post-second-dose GMTs (MNT_{50}) were 61·7 (49·5–76·9) in the 3 μg with Algel-IMDG group, 66·4 (53·4–82·4) in the 6 μg with Algel-IMDG group, and 48·0 (37·7–61·1) in the 6 μg with Algel group. Responses in the Algel-IMDG groups were not significantly different to the response in the 6 μg with Algel group. The vaccine-induced responses were similar to those observed in the convalescent

serum collected from 41 patients who had recovered from COVID-19 (figure 3B). On these 41 patients, the median titre of symptomatic patients (n=25; median 142·2 [IQR 56·6–350]) was significantly higher than that of the asymptomatic patients (n=16; 22·6 [9·0–56·5]; appendix p 16). Seroconversion rates analysed by $PRNT_{50}$ (after the second dose) were 93·4% (95% CI 83·7–97·8) in the 3 µg with Algel-IMDG group, 86·4% (75·1–93·2) in the 6 µg with Algel-IMDG group, and 86·6% (74·3–93·6) in the 6 µg with Algel group (figure 3C).

MNT_{50} wild-type neutralising antibody responses for a subset of paired serum samples (n=50) were analysed at the National Institute of Virology and Bharat Biotech (on day 28, 2 weeks after the second vaccination in all groups). Additionally, neutralising antibodies were analysed by $PRNT_{50}$ at Bharat Biotech and the National Institute of Virology. Similar results were obtained for MNT_{50} and $PRNT_{50}$ assays at both laboratories (appendix p 17). Randomly selected serum samples from day 28 were analysed by $PRNT_{50}$ at the National Institute of Virology with homologous and heterologous strain assessments. Neutralisation responses, regardless of the challenge strain, were observed (figure 3D).

In a subset of randomly selected blood samples at one site, IFN-γ ELISpot responses against SARS-CoV-2 peptides peaked at about 100–120 spot-forming cells per million peripheral blood mononuclear cells in all vaccinated groups on day 28. Both the Algel-IMDG groups elicited $CD3^+$, $CD4^+$, and $CD8^+$ T-cell responses that were reflected in the IFN-γ production, albeit in a small number of samples. However, there was a minimal detection of less than 0·5% of $CD3^+$, $CD4^+$, and $CD8^+$ T-cell responses in the 6 µg with Algel group and the Algel only group (appendix p 16).

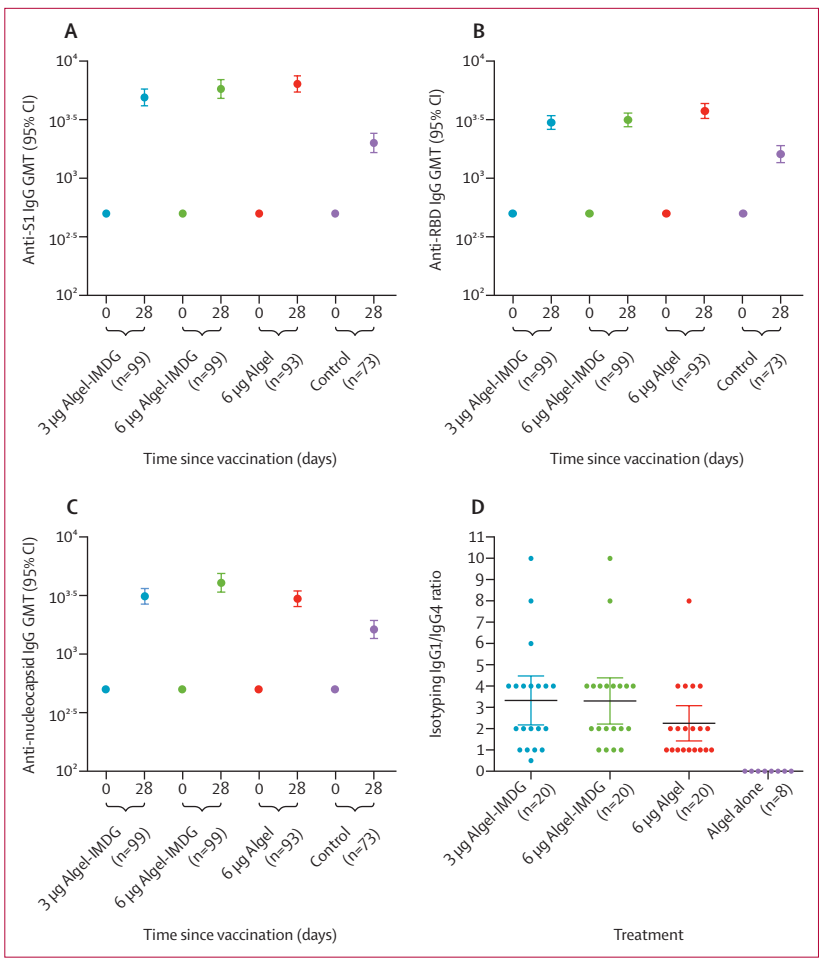

Figure 2: **SARS-CoV-2 IgG titres against anti-spike protein (A), receptor-binding domain (B), and nucleocapsid IgG (C) and anti-spike protein IgG1/IgG4 ratio (D)**
ELISA results at baseline (day 0) and 2 weeks after the second vaccination (day 28). In A–C, error bars show 95% CIs. The cutoff for detectable antibodies was 1/500. Some samples were positive for SARS-CoV-2 in the control group, as evident by the antibody titres on day 28. Endpoint titre dilution for day 28 sera samples was established with baseline (day 0), interpolated from the absorbance of the corresponding day 0 sample. Cutoff (mean ± 3 SD) for day 0 was calculated considering the absorbance of all sera dilutions (1/500 to 1/32000) tested, except the lowest dilution (1/500). ELISA titres (endpoint titres) on day 14 were not analysed. In D, the isotyping ratio was calculated (in a randomly selected subset) as IgG1/IgG4; dots show the individual datapoints and horizontal bars show means with error bars for 95% CIs. Endpoint titre=the highest sera dilution at which the absorbance was above the cutoff. GMT=geometric mean titre. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Discussion

We report the interim findings from the phase 1 clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. The vaccine was well tolerated in all dose groups with no vaccine-related serious adverse events. Both humoral and cell-mediated responses were observed in the recipients of the Algel-IMDG-based vaccines.

The most common adverse event was pain at the injection site, followed by headache, fatigue, and fever. The overall incidence of solicited local and systemic adverse events in this study was 14–21% in all vaccine-treated groups, which is noticeably lower than the rates for other SARS-CoV-2 vaccine platform candidates[18–23] and similar to the rates for other inactivated SARS-CoV-2 vaccine candidates[24,25] One serious adverse event (positive for SARS-CoV-2 by a nucleic acid test) in an individual in the 6 µg with Algel group was not related to vaccination. Because the event occurred in the 5 days after vaccination, the development of a protective immune response was not likely.

BBV152 induced binding and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates.[24,25] Titres from the Anti-spike IgG ELISA assay correlated positively with live virus microneutralisation assay titres (R^2=0·51). We assessed an accelerated schedule (vaccination 2 weeks apart) and did not include a routine schedule (vaccination 4 weeks apart). It has been reported that a routine schedule for another SARS-CoV-2 vaccine candidate offers better immune responses, as is to be expected.[26] The 4-week schedule for BBV152 3 µg and 6 µg with Algel-IMDG is being assessed in a phase 2 trial in 380 volunteers (NCT04471519). Here, we showed that all vaccine formulations were Th1 skewed with IgG1/IgG4 ratios greater than 1. Furthermore, the Algel-IMDG formulations were associated with an increase in the frequency of $CD4^+$ $INF\text{-}\gamma^+$ T cells compared with the 6 µg

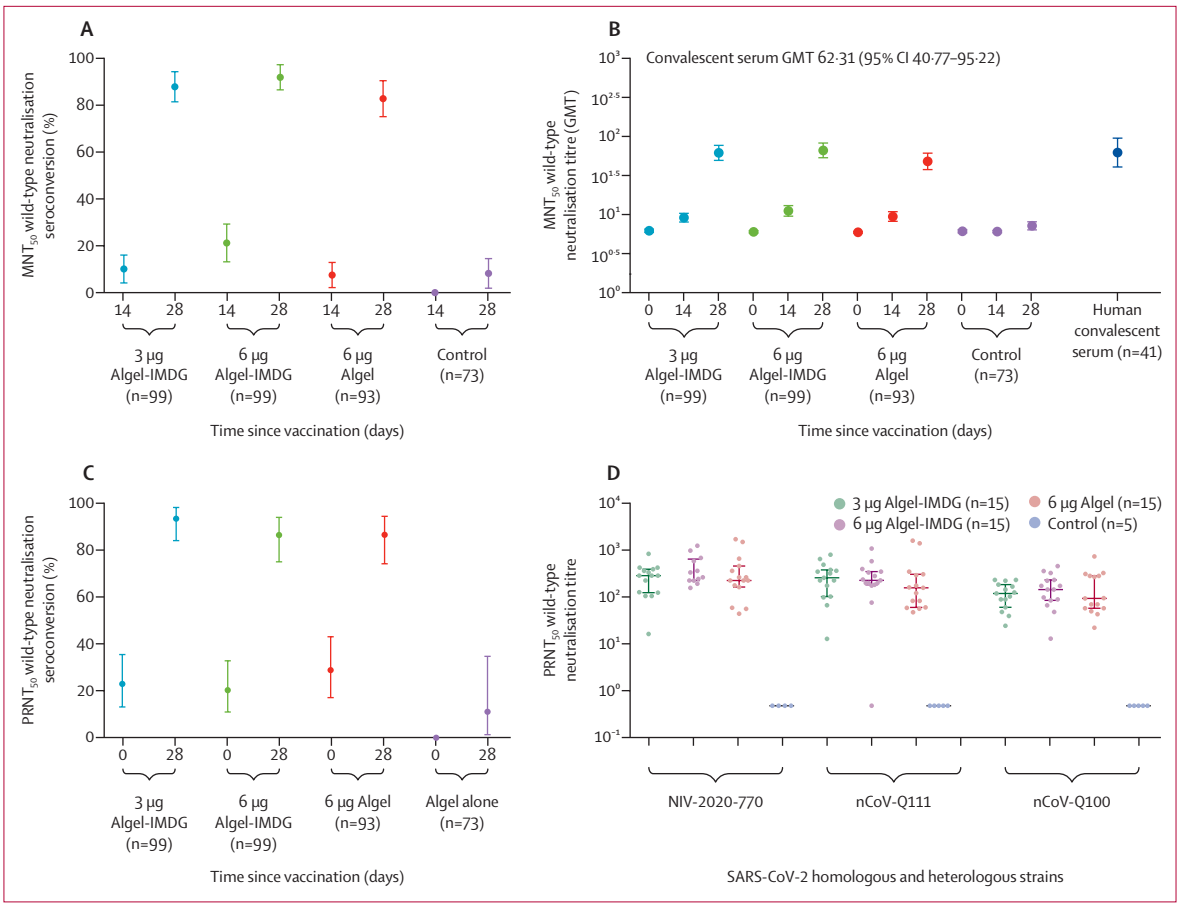

Figure 3: **SARS-CoV-2 wild-type MNT_{50} seroconversion rates (A) and GMT (B) and $PRNT_{50}$ seroconversion rates (C) and medians (D)**
Results at baseline (day 0), 2 weeks after the first vaccination (day 14), and 2 weeks after the second vaccination in the immunogenicity cohort. Seroconversion rates were defined by the proportion of titres achieving at least four-fold greater than baseline. In A–C, error bars show 95% CIs. In B, the human convalescent serum panel included specimens from participants with PCR-confirmed symptomatic or asymptomatic COVID-19, obtained at least 30 days after diagnosis (41 samples for MNT_{50}). In D, randomly selected serum samples from day 28 were analysed by $PRNT_{50}$ at the National Institute of Virology for homologous (NIV-2020-770) and heterologous (nCoV-Q11 and nCoV-Q100) assessments; dots show individual datapoints and horizontal bars show medians with error bars for IQRs. GMT=geometric mean titre. MNT_{50}=microneutralisation assay. $PRNT_{50}$=plaque-reduction neutralisation test. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

with Algel formulation, which is indicative of a Th1 bias. Additionally, cell-mediated responses from other SARS-CoV-2 inactivated vaccine candidates have not been reported thus far.

A few animal studies of SARS-CoV and Middle East respiratory syndrome-CoV inactivated or vectored vaccines adjuvanted with alum have shown Th2 responses resulting in eosinophilic infiltration in the lungs.[27–29] Adverse events might be associated with the induction of weakly neutralising or non-neutralising antibodies that lead to antibody-dependent enhancement or enhanced respiratory disease, thus prompting the attempt to develop SARS-CoV-2 vaccines that induce a $CD4^+$ Th1 response with a minimal Th2 response.[2,30–32] Whole-virion inactivated vaccines are mostly developed with Algel (alum) as the adjuvant. The response generated by alum is primarily Th2 biased, with the induction of strong humoral responses by neutralising antibodies.[33] To circumvent this concern of antibody-dependent enhancement, we have assessed this vaccine with Algel and a TLR7/8 agonist that results in immune responses that are biased to Th1. Previous studies have shown that the toll-like receptors play an integral role in bridging the innate and adaptive immune responses, leading to the differentiation of $CD4^+$ T cells into Th1 cells, which produce IFN-γ.[34] Geeraedts and colleagues[35] reported that the stimulation of TLR7 by an influenza whole-virion inactivated vaccine was a significant determinant of a greater immune response and Th1 polarisation. Thus, it is imperative to develop such whole-virion inactivated vaccines with adjuvants that can synergistically contribute to the full potential. Algel-IMDG contains an imidaquizoquinoline class TLR7/8 agonist adsorbed to Algel. Preclinical studies on BBV152 adjuvanted with this molecule reported a Th1-biased response in mice.[7] Furthermore, in a non-human primate and hamster live viral challenge studies, Algel-IMDG formulations

led to higher neutralising antibodies, which might have resulted in improved upper and lower airway viral clearance (after challenge).[8,9]

This study was done at a time of rapidly increasing daily diagnoses of COVID-19. Among all 897 individuals screened for this trial, 70 (8%) had positive SARS-CoV-2 nucleic acid test results and 63 (7%) had positive SARS-CoV-2 serology results. Seroconversion (at day 28) in the control group was reported in six (8%) of 75 participants from five separate study sites. Because substantial SARS-CoV-2 was observed at enrolment and some of the control group recipients seroconverted, post-vaccination titres from the vaccinated recipients might be slightly inflated, in the event of natural exposure to SARS-CoV-2. No symptomatic COVID-19 cases were reported in the control group.

Because this is an interim report, we are not reporting any data on the persistence of vaccine-induced antibody responses or long-term safety outcomes. The results reported here do not permit efficacy assessments. The analysis of safety outcomes requires more extensive phase 2 and 3 clinical trials. Pre-vaccination laboratory values were similar to values after vaccination. However, transient laboratory abnormalities might have been resolved by day 28. The analysis of T-cell responses by Th2 cytokines was not done and is planned for phase 2. We were unable to assess other immune responses of convalescent serum because of insufficient number of samples. The proportion of samples collected from asymptomatic individuals was high (39%), and no additional data on the severity of disease from symptomatic individuals was obtained. This study population did not have ethnic diversity and most of the participants were men, further underscoring the importance of assessing BBV152 in other populations.

However, this study has several strengths. To ensure generalisability, this study was conducted with participants from diverse geographic locations within India (appendix p 13), enrolling 375 participants across 11 hospitals. The first 50 participants were enrolled into the 3 µg with Algel-IMDG and control groups. Before granting the recommendation to proceed with the enrolment of other cohorts, masked safety data was reviewed by the data safety monitoring board. As a result, no operational bias was introduced. Despite enrolment occurring during a national lockdown, which led to several operational challenges, the overall participant retention rate was 97%. The sample size was intentionally large to enable the inference of meaningful conclusions regarding neutralising responses. With several reports questioning the efficacy of SARS-CoV-2 vaccines against antigenically divergent strains, we report neutralising responses to homologous and heterologous strains. The BBV152 vaccine strain, based on the Asp614Gly mutation, has been reported to have differential sensitivity to neutralisation by vaccine-elicited antibodies or by antibodies produced by natural infection.[36,37] The increase in Asp614Gly infectivity results in the virus being more susceptible to neutralising antibodies,[38] which is corroborated by marginal reductions in neutralising titres in the $PRNT_{50}$ assays with heterologous strains, which are devoid of the Asp614Gly mutation.

BBV152 induced binding and neutralising antibody responses and with the inclusion of the Algel-IMDG adjuvant, this is the first inactivated SARS-CoV-2 vaccine that has been reported to induce a Th1-biased response. BBV152 is stored at 2–8°C, which is compatible with immunisation cold-chain requirements. Both Algel-IMDG formulations were selected for the phase 2 immunogenicity trials. Further efficacy trials are warranted.

Contributors

RE and KMV accessed and verified the data. HJ, BG, PY, and GS led the immunogenicity experiments. KMV, SPr, VS, and RE contributed to the analysis and manuscript preparation. SR was the study coordinator and helped immensely with the protocol design and interim report generation. PA, SPr, NG, and BB contributed various neutralising antibody assays and participated in the writing of this manuscript. SPa reviewed the manuscript. PR, SV, SKR, CS, SVR, CSG, JSK, SM, VR, and RG were involved with the scientific review of this manuscript. KE was responsible for overall supervision of the project and review of the final paper.

Declaration of interests

RE, HJ, BG, KMV, SPr, VS, KE, and SR are employees of Bharat Biotech, with no stock options or incentives. KE is the Chairman and Managing Director of Bharat Biotech. PY, GS, PA, NG, SPa, and BB are employees of The Indian Council of Medical Research. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

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ANNEXURE R/5

COVAXIN 247

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Whole Virion Inactivated Corona Virus Vaccine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a single or multidose vial and injected in intra-muscular route.

Each Single human dose (0.5 mL) contains

Whole Virion Inactivated Corona Virus Antigen 6 micrograms. produced using a Vero cell-based platform, that propagates the virus, expressing the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

The vaccine is a white translucent liquid and free from extraneous particulate matter containing 6 µg of Whole Virion Inactivated Corona Virus Antigen (strain: NIV-2020-770) for injection (sterile), pH: 7.00 - 8.00.

4. CLINICAL PARTICULARS

It is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 18 years of age and older. The use of this vaccine should be in accordance with official recommendations. This vaccine is permitted for restricted use in Emergency situation in Clinical Trial mode, as per provisions of New Drugs and Clinical Trials Rules, 2019, under Drugs & Cosmetics Act 1940.

4.1 Therapeutic indication

COVAXIN™ is indicated for active immunization against SARS-CoV-2 Virus infection for age ≥18years.

4.2 Posology and method of administration.

COVAXIN™ should be administered as two doses on Day 0 and Day 28.
Method of administration: intramuscular injection (IM).

4.3 Contraindications

- Hypersensitivity to any constituents of the vaccine.
- Pregnant and lactating mothers.
- During fever or severe infection.
- Individuals below 18 years.

4.4 Special warnings and precautions for use

- Do not administer intravenously, intradermally, or subcutaneously.
- Like all other vaccines, supervision and appropriate medical treatment should always be available to treat any anaphylactic reactions following immunization.
- The vaccine should remain under medical supervision for at least 30 minutes after vaccination.

Before use, COVAXIN™ should be shaken well to obtain a uniform, whitish translucent suspension. Vial should be visually checked for the presence of any particulate matter or other coloration, if any, prior to its administration. If in doubt, do not use the contents of the vial.

COVAXIN™ should not be mixed with other vaccines.

4.5 Interaction with other medicinal products.

Chloroquine and Corticosteroids as they may impair the antibody response.

4.6 Pregnancy and Lactation

Safety and effectiveness have not been established in pregnant women and in nursing mothers.

4.7 Effects on ability to drive and use machines

No studies on the effect of COVAXIN™ on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trial Experience

Safety of the COVAXIN™ vaccine was established in Phase 1 and Phase 2 studies.

Phase 1 clinical trial was conducted in India in 375 adult healthy volunteers. The most common local adverse event reported was Injection site Pain. The most common systemic adverse events reported were headache, followed by fatigue, fever, body ache, abdominal pain, nausea, and vomiting. The other less common adverse events were dizziness/giddiness, tremor, sweating, cold, cough, and injection site swelling. No vaccine related serious adverse events (SAE) were reported.

A Phase 2 clinical trial was conducted in India in 380 adolescents and adult healthy volunteers. Similar adverse events were reported in the phase 2 clinical trial. No serious adverse events (SAE) were reported.

A Phase 3 efficacy study is on-going in 25,800 participants and administered with 1st dose of vaccination with COVAXIN™, no vaccine related adverse events were observed.

4.9 Immune Response

COVID-19 disease is caused due to SARS-CoV-2 virus infection.

In Phase 1 clinical trial a total of 375 healthy participants were enrolled across the three groups and received three vaccine formulations, BBV152A (3µg with Algel-IMDG (Aluminium hydroxide gel- Imidazo quinolin gallamide (IMDG); a TLR 7/8 agonist), BBV152B (6µg with Algel-IMDG), and BBV152C (6µg with Algel). None of the participants had detectable neutralizing antibodies at baseline analyzed by MNT_{50}. The proportion of participants seroconverted post 2 weeks after 2nd dose was 87.9%, 91.9%, and 82.8% in the BBV152A, B, and C groups, respectively.

In Phase 2 clinical trial a total of 380 healthy participants were enrolled among two groups and received two vaccine formulations, BBV152 A and BBV152B. None of the participants had detectable neutralizing antibodies at baseline analyzed by MNT_{50}. The proportion seroconverted participants of Group 1 and Group 2, post 4 weeks of 2nd dose was 88.0% and 96.6% respectively.

4.10 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

COVID-19 disease is caused due to SARS-CoV-2 virus infection. **COVAXIN™** is a whole virion inactivated SARS-CoV-2 virus vaccine, has been studied in Phase 1 and 2 clinical studies for safety and immunogenicity and found to be safe and immunogenic. **COVAXIN™** has been shown to prevent COVID-19 following 2 doses given 4 weeks apart. The duration of protection against COVID-19 is currently unknown.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

All the formulations were tested for immunogenicity in mice, rats, and rabbits. Mice, rats, and rabbits were vaccinated on days 0, 7, and 14 (n+1 doses). Further these formulations are tested for immunogenicity, safety, and protective efficacy in Syrian Hamster challenge model and Non-Human Primates (*Rhesus macaque*) challenge model. The Hamsters were vaccinated on Days 0, 14, and 35 (n+1 doses), the live SARS-CoV-2 virus was challenged through intranasal route on Day 50. Likewise, the Rhesus macaques were vaccinated on Days 0 and 14, and live SARS-CoV-2 virus was challenged through intranasal and intratracheal routes on Day 28. All the formulations were found to be safe, immunogenic, and provided effective protection to both upper and lower respiratory tract.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients and composition

Each 0.5 mL (single human dose) contains

Whole Virion Inactivated Corona Virus Antigen …….6 µg

Aluminium hydroxide gel equivalent to Al^{+3}……...250 µg

TLR 7/8 Agonist……15 µg

2-phenoxyethanol……...2.5 mg

Phosphate buffered saline……..q.s. to 0.5 mL

Note: TLR 7/8 agonist is an Imidazo quinolin gallamide (IMDG)

6.2 Incompatibilities

The product should not be mixed with any other medicinal products or active immunizing agents.

6.3 Shelf life

The expiry date of COVAXIN™ is indicated on the label and carton of the product. Do not use the product after the expiration date shown on the label and carton of the product.

6.4 Special precautions for storage

Store at +2° to +8 °C, do not freeze. Discard if frozen.

Shake well before use. Keep out of reach of children. Protect from light.

Do not use the vaccine after the expiration date as shown on the label.

6.5 Nature and contents of container

COVAXIN™ is presented as Single dose (0.5 mL) and multidose (5 mL and 10 mL) in transparent vial (type I glass) with a stopper (butyl rubber) and a flip-off plastic cap with aluminium seal. Each vial of single dose contains 0.5 mL, each vial of multidose contains 10 doses (5 mL) and 20 doses (10 mL) respectively.

6.6 Handling of multi-dose vials

Opened vials should be used as soon as possible and within 6 hrs when kept between 2 - 8 ºC.

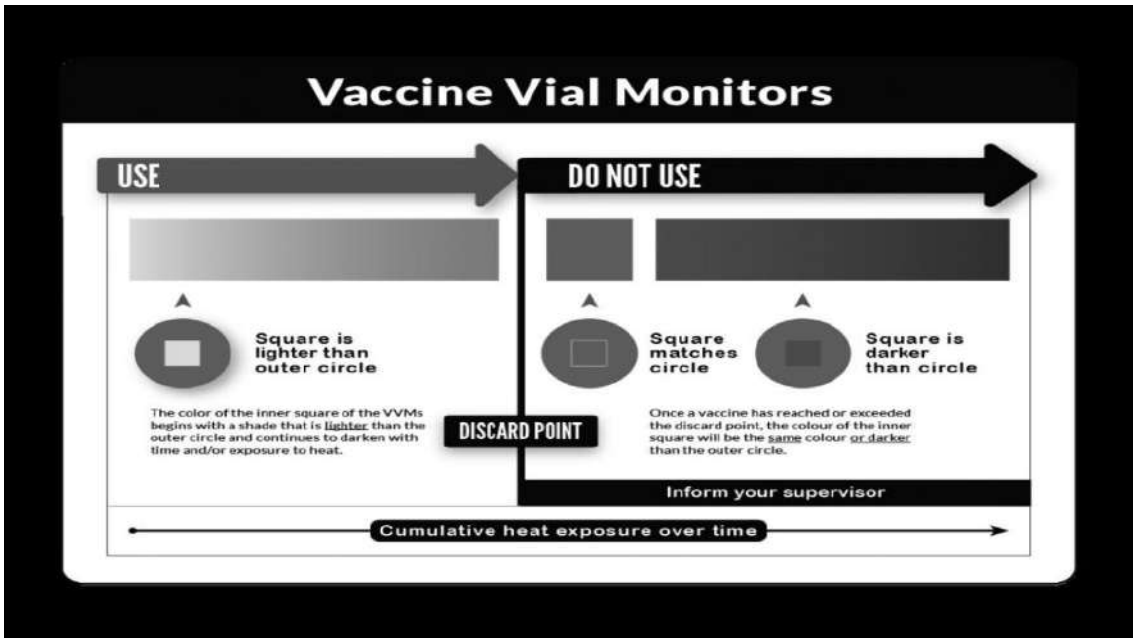
Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. THE VACCINE VIAL MONITOR (OPTIONAL)

Presentation available with or without vaccine vial monitor

Vaccine Vial Monitors (VVM7) dot is a part of the label on **COVAXIN™** vials supplied through Bharat Biotech. VVM7 are supplied by TEMPTIME Corporation, USA. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.



The interpretation of the VVM7 is simple: Focus on the central square; its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, the vial should be discarded.

8. MARKETING AUTHORISATION NUMBER(S)

MF/BIO/21/000002, dated 3rd Jan, 2021

9. MARKETING AUTHORISATION HOLDER

Manufactured and Marketed by:

Bharat Biotech International Ltd.

Sy. No. 230, 231 and 235, Genome Valley, Turkapally, Shamirpet Mandal, Medchal-Malkajgiri District - 500 078, Telangana State, India.
E-mail: feedback@bharatbiotech.com; Website: www.bharatbiotech.com
For complaints and suggestions about the product, and any adverse event,
please email to feedback@bharatbiotech.com or call on Toll-free number: 1800 102 2245

10. DATE OF CREATION / REVISION OF THE TEXT

15th January, 2021

FACT SHEET FOR VACCINE RECIPIENTS AND CAREGIVERS

RESTRICTED USE OF COVAXIN™ UNDER CLINICAL TRIAL MODE

THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19)

PRIORITIZED GROUPS OF INDIVIDUALS WHO HAVE BEEN INFORMED BY THE MINISTRY OF HEALTH & FAMILY WELFARE TO ATTEND A BOOTH SPECIFIED FOR COVAXIN™ BASED VACCINATION

You are being offered the Bharat Biotech COVID-19 Vaccine (**COVAXIN™**) to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. This Fact Sheet contains information to help you understand the risks and benefits of the Bharat Biotech COVID-19 Vaccine (**COVAXIN™**).

Reporting of side effects

As with any new medicine, this vaccine will be closely monitored to allow quick identification of any new safety information. You can help by reporting any side effects you may get after vaccination to Bharat Biotech who is the manufacturer of COVAXIN™ vaccine on 24x7 Toll-Free Number: 18001022245 or at email pvg@bharatbiotech.com. For more information, please read this Information Sheet carefully.

Please read this Fact Sheet for information about the Bharat Biotech COVID-19 Vaccine (COVAXIN™). Talk to Vaccinator/ Officer supervising your vaccination if you have any questions. It is your choice to receive the Bharat Biotech COVID-19 Vaccine (COVAXIN™). The Bharat Biotech COVID-19 Vaccine (COVAXIN™) is administered as a 2-dose series, 4 weeks apart, into the deltoid muscle of the upper arm.

WHAT IS COVID-19?

COVID-19 disease is caused by a Coronavirus called SARS-CoV-2. This type of Coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 may experience wide range of symptoms of mild to severe category. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; loss of taste or smell of recent onset; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

WHAT IS THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

The Bharat Biotech COVID-19 Vaccine (**COVAXIN™**) is a vaccine with approval for restricted use in emergency situation that may prevent COVID-19. The Central Licensing Authority has granted permission for the sale or distribution of COVAXIN for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode.

In phase 1 and phase 2 clinical trials, COVAXIN™ has demonstrated the ability to produce antibodies against COVID-19. However, the clinical efficacy of COVAXIN is yet to be established and it is still being studied in phase 3 clinical trial. Hence, it is important to appreciate that receiving the vaccine does not mean that other precautions related to Covid-19 need not be followed.

WHERE WILL MY VACCINATION INFORMATION BE RECORDED?

The Vaccinator/ Officer supervising your vaccination may include your vaccination information in your state/National Immunization Information System or another designated system. This will ensure that you receive the same vaccine when you return for the second dose. Please also note that privacy and confidentiality pertaining to any information provided by you and archived in the National Immunization Information System will be maintained.

WHAT IS RESTRICTED USE IN EMERGENCY SITUATION?

COVAXIN™ is permitted for restricted use in emergency situation under Clinical Trial Mode. This means that the vaccine offered under this plan will be offered to the restricted prioritized groups only. As you fell under this category, you have been invited to this booth for administration of COVAXIN. This administration will take place under clinical trial mode, which is different from clinical trial as effect of COVAXIN will not be examined against any other intervention through this effort. You will be monitored for any adverse event under this clinical trial mode and supported for medical care under the existing public health program.

WHAT SHOULD YOU MENTION TO YOUR VACCINATION PROVIDER BEFORE YOU GET THE COVAXIN™ COVID-19 VACCINE?

Tell the Vaccinator/ Officer supervising your vaccination about all of your medical conditions, including if you:

- Are you on regular medication for any illness? If yes, for how long and for which condition?

- Have any allergies
- Have fever
- Have a bleeding disorder or are on a blood thinner
- Are immunocompromised or are you on a medicine that affects your immune system
- Are pregnant
- Are breastfeeding
- Have received another COVID-19 vaccine

It is advisable not to take the vaccine in any of these conditions

WHO IS ELIGIBLE TO GET THE BHARAT BIOTECH COVID-19 VACCINE?

CDSCO has authorized the Restricted Use of COVAXIN™ under Clinical Trial Mode. Individuals who are prioritized under the public health program of the Ministry of Health & Family Welfare, Government of India will be covered under this endeavor. Informing the individuals about the offer for vaccination with COVAXIN will rest with the respective Government Program Officials. Those offered COVAXIN at

pre-specified booths will have the options to receive or reject administration of the vaccine.

WHO SHOULD NOT GET BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

You should not get the BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) if you:

- Have any history of allergies.
- Have fever.
- Have a bleeding disorder or are on a blood thinner.
- Are immune-compromised or are on a medicine that affects *your* immune system
- Are pregnant.
- Are breastfeeding.
- Have received another COVID-19 vaccine.
- Any other serious health related issues, as determined by the Vaccinator/Officer supervising vaccination.

WHAT ARE THE INGREDIENTS IN THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

The BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) includes the following ingredients: COVAXIN™ contains 6µg of whole-virion inactivated SARS-CoV-2 antigen (Strain: NIV-2020-770), and the other inactive ingredients such as aluminum hydroxide gel (250 µg), TLR 7/8 agonist (imidazoquinolinone) 15 µg, 2-phenoxyethanol 2.5 mg, and phosphate buffer saline up to 0.5 ml. The vaccine (COVAXIN™) thus has been developed by using inactivated/killed virus along with the aforementioned chemicals.

HOW IS THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) GIVEN?

The BHARAT BIOTECH COVID-19 VACCINE will be given to you as an injection into the deltoid muscle of the upper arm. The BHARAT BIOTECH COVID-19 VACCINE **(COVAXIN™)** vaccination series is 2 doses given 4 weeks apart.

HAS BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) BEEN USED BEFORE?

The Central Licensing Authority has granted permission for the sale or distribution of COVAXIN™ for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode. In phase 1 and Phase 2 clinical trials, about 680 (300 in Phase 1, and 380 in Phase 2) were administered with 2-doses of COVAXIN™. Phase 3 clinical trial is ongoing in 25,800 participants, and all the participants have received the first dose, as on 06th Jan 2021.

WHAT ARE THE BENEFITS OF BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

In an ongoing clinical trial, the BHARAT BIOTECH COVID-19 VACCINE **(COVAXIN™)** has been shown to generate immunity following 2 doses given 4 weeks apart.

However, the clinical efficacy of COVAXIN is yet to be established and it is still being studied in phase 3 clinical trial. Hence, it is important to appreciate that receiving the vaccine does not mean that other precautions related to Covid-19 need not be followed.

WHAT ARE THE RISKS OF BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?
Side effects that have been reported with the BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) include:

- Injection site pain
- Injection site swelling
- Injection site redness
- Injection site itching
- Stiffness in the upper arm
- Weakness in injection arm
- Body ache
- Headache
- Fever
- Malaise
- Weakness
- Rashes
- Nausea
- Vomiting

There is a remote chance that the BHARAT BIOTECH COVID-19 VACCINE (**COVAXIN™**) could cause a severe allergic reaction. A severe allergic reaction may very rarely occur after getting a dose of the BHARAT BIOTECH COVID-19 VACCINE (**COVAXIN™**). For this reason, your vaccination provider will ask you to stay for 30 minutes after each dose of vaccination at the place where you received your vaccine for monitoring after vaccination. Signs of a severe allergic reaction can include:

- Difficulty in breathing
- Swelling of your face and throat
- A fast heart beat
- Rash all over your body
- Dizziness and weakness

These may not be all the possible side effects of the BHARAT BIOTECH COVID-19 VACCINE (**COVAXIN™**). Serious and unexpected side effects may occur. BHARAT BIOTECH COVID-19 VACCINE (**COVAXIN™**) is still being studied in clinical trials.

WHAT SHOULD I DO ABOUT SIDE EFFECTS?

If you experience any side effect(s), please contact/visit your health provider/Vaccinator/ Officer supervising your vaccination or immediately go to the nearest hospital.

WHAT IF I DECIDE NOT TO GET THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™)?

It is your choice to receive or not to receive the BHARAT BIOTECH COVID-19 VACCINE (**COVAXIN™**).

CAN I RECEIVE THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) WITH OTHER VACCINES?

There is no scientific information yet available on the appropriateness of use of the BHARAT BIOTECH COVID-19 VACCINE (**COVAXIN™**) along with other vaccines.

WHAT IF I AM PREGNANT OR BREASTFEEDING?

If you are pregnant or breastfeeding, you should not get the vaccine as the effect of the vaccine has not been studied in pregnant women and nursing mothers.

WILL THE BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) GIVE ME COVID-19?

No. BHARAT BIOTECH COVID-19 VACCINE (COVAXIN™) is an inactivated (killed) vaccine, and hence, there is no chance of getting COVID-19 because of COVAXIN™ vaccination.

HOW LONG WILL I HAVE TO PARTICPATE IN THIS PROGRAM?

All the Vaccine recipients will be followed-up for a period of 3 months after the 2nd dose of vaccination.

In case of any serious adverse events, Vaccine recipients will be provided medically recognized standard of care in the government designated and authorized centers/hospitals. The compensation for serious adverse event will be paid by sponsor (BBIL) if the SAE is proven to be causally related to the vaccine. The compensation will be determined by the ICMR Central Ethics Committee, as appropriate.

All the recipients need to report to the health care provider/site/sponsor, if they are having signs and symptoms of COVID-19 or diagnosed with COVID-19. If any Vaccine recipient develops symptoms of COVID-19, Vaccine recipient will be provided medically recognized standard of care in the government designated and authorized centers/hospitals. COVID-19 Positive outcomes must be documented in Adverse Event Form. Proof of positive RT-PCR (tests conducted under the existing government program and from approved laboratories) should be provided to establish the diagnosis of COVID-19. Vaccine recipient's verbal recall will not confirm the diagnosis.

COVID-19 VACCINATION (COVAXIN™)
SCREENING & CONSENT FORM

The COVID-19 Vaccine, COVAXIN™, is being offered to you as part of a vaccination drive by the Ministry of Health and Family Welfare under restricted use in emergency situation. COVAXIN™ is being offered at this booth in this district.

The Bharat Biotech COVID-19 Vaccine (**COVAXIN™**) is a vaccine with approval for restricted use in emergency situation that may prevent COVID-19.

In phase 1 and phase 2 clinical trials, COVAXIN™ has demonstrated the ability to produce antibodies against COVID-19. However, the clinical efficacy of COVAXIN is yet to be established and it is still being studied in phase 3 clinical trial. Hence, it is important to appreciate that receiving the vaccine does not mean that other precautions related to Covid-19 need not be followed.

The Central Licensing Authority has granted permission for the sale or distribution of COVAXIN for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode.

In case of any adverse events or serious adverse events, you will be provided medically recognized standard of care in the government designated and authorized centers/hospitals.

The compensation for serious adverse event will be paid by sponsor (BBIL) if the SAE is proven to be causally related to the vaccine.

HOW CAN YOU LEARN MORE IF YOU WISH BEFORE PROVIDING CONSENT?

- Ask the Vaccinator/ Officer supervising your vaccination.
- Visit at https://www.mygov.in/covid-19/

I FUTHER EMPHASIZE THAT ANY INFORMATION PROVIDED BY ME PRIOR TO TAKING THE VACCINE WILL BE ARCHIVED IN THE DATABASE MAINTAINED BY THE IMMUNIZATION PROGRAM OF THE GOVERNMENT & PRIVACY AS WELL AS CONFIDENTIALITY OF THE INFORMATION PROVIDED BY YOU WILL BE MAINTAINED.

Recipient Name:		
DOB: Age:	Gender: Male…….. Female……..Third Gender…..	Marital Status:
ID Number / Aadhaar Number/Registration Number:		
Address of the recipient: Mobile/Phone Number:		
Name: Mobile/Phone Number:		
Name and Address of Clinic/Office Site Where Vaccine is Administered:		
Name and contact mobile number of the Vaccinator/ Officer supervising your vaccination:		

S. No.	**Questionnaire**			
1.	Are you feeling sick today?	□ Yes	□ No	
2.	In the last 14 days, have you had a COVID-19 test or been told by a health care provider or health department to isolate or quarantine at home due to COVID-19 infection or exposure?	□ Yes	□ No	□ Unknown
3.	Have you been treated with antibody therapy for COVID-19 in the past 90 days (3 months)? If yes, when did you receive the last dose as furnished on document? …….....(please tell me)	□ Yes	□ No	□ Unknown
4.	Have you ever had a serious allergic reaction?	□ Yes	□ No	□ Unknown
5.	Have you had any vaccines in the past 28 days (4 weeks)? If yes, how long ago was your most recent vaccine? …….....(please tell me)	□ Yes	□ No	□ Unknown
6.	Are you pregnant or considering becoming pregnant?	□ Yes	□ No	□ Unknown
7.	Are you a nursing mother?	□ Yes	□ No	□ Unknown
8.	Are you on any medication for a long-standing disease? a) If yes please tell me the name of the disease …….	□ Yes	□ No	□ Unknown
9.	Are you taking radiotherapy?	□ Yes	□ No	□ Unknown

INFORMED CONSENT

I have been provided and have read, or had been explained to me, the Fact sheet about the COVID-19 vaccination. I understand that this vaccine requires two doses for it to be effective and two doses need to be administered. I have been allowed to ask questions which were answered to my satisfaction. I understand the benefits and risks of the vaccination as described. I request that the COVID-19 vaccination be given to me.

Name	**Vaccine recipient (Signature/Thumb impression)**	**Date/Time**

If vaccine recipient is illiterate, consent should be taken in the presence of Impartial Witness and also please include Impartial Witness Signature.

Name	**Impartial Witness (Signature)**	**Date/Time**

Area Below to be Completed by Vaccinator					
Vaccine Name	Vaccine Dose	Date of administration	Time of Administration	Route of Administration	Manufacturer & Lot Number
COVAXIN™	□ First Dose				
	□ Second Dose				

Administration Site:	□ Left Deltoid	□ Right Deltoid
Dosage:	□ 0.5ml	Intra Muscular

I have reviewed the details of side effects with the vaccine recipient.

I confirm that the vaccine recipient was allowed to ask questions about the vaccination, and all the questions asked by the vaccine recipient have been answered correctly, and to the best of my ability.

Name of the Vaccinator: _____

Vaccinator Signature: _____

Location Name (Vaccination Site): _____

Please contact your vaccination supervising officer at this number ……and your vaccinator (contact number ……..) in case of any need related to vaccination or difficulty faced even after going back home following vaccination.

ANNEXURE R/6

File No: BIO/CT/20/000077

Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FORM CT-06

(See rules 22, 25, 26, 29 and 30)

PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licencing Authority hereby permits M/s Bharat Biotech International Limited, Genome Valley, Shameerpet (India) -500078, Telephone No.: 9848887849, Fax: 04023480560, E-Mail: dra@bharatbiotech.com to conduct clinical trial of the new drug or investigational new drug, Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) as per **protocol no.:BBIL/BBV152-A/2020, Version No: 2.0, Date: 26-06-2020** in the below mentioned clinical trial sites.

CT No.: CT- 14/2020

2. Details of new drug or investigational new drug and clinical trial site [As per Annexure].

3. This permission is subject to the conditions prescribed in part A of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

Place: New Delhi
Date: 29.06.2020

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority

Annexure:

Details of New Drug or Investigational New Drug:

Name of the new drug or investigational new drug:	Whole Virion Inactivated Corona Virus Vaccine, [BBV152]			
Therapeutic class:	Vaccine			
Dosage form:	Liquid (Injection for Intramuscular route)			
Composition:	Each dose of 0.5 ml contains			
	Active ingredient	**Quantity**		
	Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770)	3 mcg	6 mcg	6 mcg
	Inactive ingredients			
	Aluminium Hydroxide gel equivalent to Al+++	250 mcg	250 mcg	250 mcg
	TLR6 Agonist	15 mcg	15 mcg	---
	2-Phenoxyethanol (2PE) I.P.	2.5 mg	2.5 mg	2.5 mg
	Phosphate Buffered Saline	Qs to 0.5 ml	Qs to 0.5 ml	Qs to 0.5 ml
Indications:	For active immunization against Corona Virus infection (SARS-COV-2) COVID-19.			

Details of clinical trial sites-

S. No.	Name and Address of Clinical Trial Site	Ethics Committee details	Name of Principal Investigator
1	Dr.. Pandit B D Sharma PGIMS, Rohtak, Haryana.	Institutional Ethics committee, PGIMS, Rohtak, Haryana. ECR/293/Inst/HR/2013/RR-19	Dr. Savita Verma,
2	All India Institute of Medical Sciences AIIMS, Ansari Nagar, 110029 New Delhi	Ethics Committee AIIMS, Ansari Nagar, 110029 New Delhi. ECR/547/INST/DL/2014/RR-17	Dr. Sanjay Kumar Rai
3	King George Hospital, Visakhapatnam, Andhra Pradesh. 530002.	Institutional Ethics committee, King George Hospital, Visakhapatnam, AP. ECR/261/KGH/Inst/AP/2013/RR-20	Dr. Vasu Dev
4	Jeevan Rekha Hospital, Dr. B R Ambedkar Road Belgaum, Karnataka.	Institutional Ethics committee, Jeevan Rekha Hospital, Belgaum, Karnataka. ECR/1242/INST/KA/2019	Dr. Amit Bhate
5	Gillurkar Multispeciality Hospital,20, Reshimbag, Umred Road Nagpur, Maharashtra. 440009	Gillurkar Hospital Ethics committee, Nagpur, Maharashtra. 440009 ECR/1374/INST/MH/2020	Dr. Chandrashekar Gillurkar
6	All India Institute of Medical Sciences, Patna. 801507.	Institutional Ethics committee, All India Institute of Medical Sciences, Patna 801507. ECR/1387/INST/BR/2020	Dr. C. M Singh,

7	Rana Hospital and Trauma center, Rail Vihar Medical college road, Chargawa Gorakhpur, UP. 273001	Institutional Ethics committee, Rana Hospital and Trauma center, Rail Vihar Medical college road, Chargawa Gorakhpur, UP. 273001 ECR/1332/INST/UP/2020	Dr. Ajeet Pratap Singh
8	Institute of Medical sciences & SUM Hospital, K 8, Kalinga Nagar, Ghatikia,Bhubaneshwar - 751003, Odisha	Institutional Ethics committee, IMS, SUM Hospital, K 8, Kalinga Nagar, Ghatikia,Bhubaneshwar - 751003, Odisha.	Dr. Venkat Rao
9	Redkar Hospital, Oxelbag, Dhargal GOA 403513	Institutional Ethics committee, Redkar Hospital, Oxelbag, Dhargal GOA403513 ECR/902/INST/GA/2018	Dr. Sagar Vivek Redkar
10	Prakhar Hospital, 8/219 Arya Nagar, Kanpur UP 208002	Ethics committee, Prakhar Hospital, 8/219 Arya Nagar, Kanpur UP 208002 ECR/1017/INST/UP/2017	Dr. Jitendra Kushwaha
11	SRM Hospital & Research center, SRM Nagar, Potheri, Kattaankulathur Tamil Nadu 603203	Institutional Ethics committee, SRM Hospital & Research center, SRM Nagar, Potheri, Kattaankulathur Tamil Nadu 603203 ECR/431/INST/TL/2013/RR-19	Dr. Satyajit Mohapatra
12	Nizams Institute Medical Sciences & Hospital,Punjagutta Hyderabad, Telangana	Institutional Ethics committee, Nizams Institute Medical Sciences& Hospital, Punjagutta Hyderabad, Telangana ECR/303/INST/AP/2013/RR-19	Dr. Prabhakar Reddy
13	KR Hospital Mysuru Medical Collage, Karnataka	Ethics committee, KR Hospital Mysuru Medical Collage,KarnatakaEC/RENEW/INST/KA/2013/RR-19	Dr. Madhu Kumar R

In addition to point 3, the permission is subject to following condition(s):

I. Firm is required to conduct Phase I/II clinical trial as per protocol titled "Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers" vide Protocol No: BBIL/BBV152-A/2020 Version No: 2.0 Date: 26-06-2020 after approval of Ethics committee.

II. Clinical trial participating sites should have facilities to handle emergency situations such as anaphylaxis

III. The principal investigators should have appropriate qualification & experiences suitable for the conduct of study.

IV. Firm is required to submit results of Phase I clinical trial to the DCGI before initiating the Phase-II study.

V. Firm is required to submit following information/documents & initiate the trial on satisfactory results:

   a. Additional animal toxicity data on other species as and when the studies are completed.

   b. Certificate of analysis of Drug product including adventitious agents and Hemadsorption results along with specification and results of TLR7 in drug product shall be submitted before initiation of clinical trial.

c. Further stability data for batches used for animal toxicity & ongoing stability data of CT batches (accelerated & real time) shall be submitted regularly.
d. Copy of receipt of strain from NIV, Pune and MoU with NIV, if any.
e. Contract entered by the sponsor with the investigator/institutions with regard to financial support, amount of fees, honorarium, payments in kind etc. to be paid to the investigator.

VI. The batches for use in the clinical trial shall be parallely tested at CDL, Kasauli.

Place: New Delhi
Date: 29.06.2020

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority

File No: BIO/CT/20/000077
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

From:

The Drugs Controller General, India
Directorate General of Health Services,

FDA Bhawan, Kotla Road,
New Delhi-110002

To

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderaba, India -500 078.

Subject: Permission for conducting a Phase I/II clinical trial titled "Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers" vide Protocol No: BBIL/BBV152-A/2020 Version No: 2.0 Date: 26-06-2020.- regarding.

Reference: Your Application No. BIO/CT04/FF/2020/20104 dated 12-JUN-2020 on the subject mentioned above.

Sir,

Please refer to your application no. BIO/CT04/FF/2020/20104 dated 12-JUN-2020, received by this office on the above subject. Please find enclosed herewith permission to conduct a Phase IIa study in Form CT-06 under the New Drugs and Clinical Trials Rules, 2019 along with the details of new drug and clinical trial sites.

Please acknowledge receipt of the same.

Yours faithfully,

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority

FULL DETAILS (Read-only)

CTRI Number	**CTRI/2020/07/026300** [Registered on: 01/07/2020] **Trial Registered Prospectively**
Last Modified On:	17/03/2021
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Vaccine
Study Design	Randomized, Parallel Group, Active Controlled Trial
Public Title of Study	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers
Scientific Title of Study Modification(s)	An Adaptive, Seamless Phase 1, Followed by Phase 2 Randomized, Double-blind, Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability and Immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) in Healthy Volunteers

Secondary IDs if Any Modification(s)

Secondary ID	Registry
BBIL/BBV152-A/2020; Version 3.0; Date 07-07-2020	Protocol Number

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Name	Dr V Krishna Mohan
Address	Bharat Biotech International Ltd, Medical Affairs Department, Genome Valley, Shameerpet Medchal TELANGANA 500078 India
Phone	04023480567
Fax	04023480560
Email	kmohan@bharatbiotech.com

Details Contact Person Scientific Query

Name	Dr V Krishna Mohan
Address	Bharat Biotech International Ltd, Medical Affairs Department, Genome Valley, Shameerpet Medchal TELANGANA 500078 India
Phone	04023480567
Fax	04023480560
Email	kmohan@bharatbiotech.com

Details Contact Person Public Query

Name	Dr V Krishna Mohan
Address	Bharat Biotech International Ltd, Medical Affairs Department, Genome Valley, Shameerpet Medchal TELANGANA 500078 India
Phone	04023480567
Fax	04023480560
Email	kmohan@bharatbiotech.com

Source of Monetary or Material Support Modification(s)

Bharat Biotech International Ltd Genome Valley Shameerpet Hyderabad – 500 078 Telagana INDIA

Primary Sponsor

Name	Bharat Biotech International Limited
Address	Bharat Biotech International Ltd, Medical Affairs department, Genome Valley, Shameerpet, Medchal, TELANGANA - 500078 India
Type of Sponsor	Pharmaceutical industry-Indian

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

India

Sites of Study
Modification(s)

No of Sites = **12**

Contact Person	Name of Site	Site Address	Phone/Fax/Email
Dr Chandramani Singh	All India Institute of Medical Sciences	Room No. 17 Department of Community & Family Medicine All India Institute of Medical Sciences, Aurangabad Road Phulwari Sharif Patna	9931733280 drcmsingh@aiimspatna.org
Dr Sanjay Kumar Rai	All India Institute of Medical Sciences	Room No. 29 Department of Center for Community Medicine All India Institute of Medical Sciences, Ansari Nagar New Delhi	09868397358 drsanjay.aiims@gmail.com
Dr Chandrasekhar Gillurkar	Gillukar Multispeciality Hospital	20, Reshimbagh, Umred road, Nagpur - 440009 Nagpur MAHARASHTRA Nagpur	09890005678 cgillurkar@yahoo.com
Dr Venkata rao	Institute of Medical Sciences and SUM Hospital	DEPARTMENT OF COMMUNITY MEDICINE, 3rd Floor, K-8, KALINGA NAGAR, GHATIKIA, Jajapur	07853889552 e.venkata.rao@gmail.com
Dr Amit Suresh Bhate	Jeevan Rekha Hospital	3rd Floor Room No. 2 Jeevan Rekha Hospital, Dr. B.R. Ambedkar Road Opposite Civil Hospital Belgaum	9695237796 jrhclinicalresearch@gmail.com
Dr R Vasudev	King George Hospital	Dept of Medicine, 1st floor, King george Hospital, Maharanipeta Visakhapatnam	9866739808 vasudev.kgh@gmail.com
Dr Prabhakar Reddy	Nizam's Institute of Medical Sciences	NIMS Old Block,ward No 11,second floor, near ward no 11 opp NP@ Department of	7416512888 cptnims@gmail.com

			Clinical Pharmacology & Therapeutics, (CP&T) Hyderabad	
	Dr Savita Verma	PGIMS	Room no 428,Department of Pharmacology Directorate Office Rothak,Pt BD SHARMA,PGIMS/UHS. Rohtak	9812283746 verma.savi@gmail.com
	Dr Jitendra Kushwaha	Prakhar Hospital	4th Floor Research Room Prakhar Hospital Pvt Ltd. 8/219 Arya Nagar Kanpur Nagar	08448522450 principalinvestigator1177@gmail.com
	Dr Ajeet Pratap Singh	Rana Hospital and Trauma Center	Room No. 7 Rana Hospital Pvt. Ltd. Rail Vihar Medical College Road Chargawa Gorakhpur	7652456810 ajeetpsingh1177@gmail.com
	Dr Sagar Vivek Redkar	Redkar Hospital and Research Centre	Room No. 11 Mumbai Goa Highway, Oshalbag Village Dhargal, Tal North Goa	07776084679 redkar.research@gmail.com
	Dr Satyajit Mohapatra	SRM Hospital & Research center	Department of Pharmacology , SRM Medical College Hospital and Research Centre, Kattankulathur Campus Kancheepuram	09791161626 satyajitmp@gmail.com

Details of Ethics Committee
Modification(s)

No of Ethics Committees= **11**

Name of Committee	Approval Status
Ethics Committee, All India Institute of Medical Sciences, Delhi	Approved
Ethics Committee, Prakhar Hospital Pvt Ltd,Kanpur	Approved
Gillurkar Hospital Ethics Committee, Nagpur	Approved
Institutional Ethics Committee, All India Institute of Medical Sciences, Patna	Approved
Institutional Ethics Committee, IMS & SUM Hospital,odissha	Approved
Institutional Ethics Committee, Jeevan Rekha Hospital, Belgavi	Approved
Institutional Ethics Committee, PGIMS, Rohtak	Approved
Institutional Ethics Committee, Rana Hospital Pvt Ltd, Gorakhpur	Approved
Institutional Ethics Committee, SRM College Hospital and Research Centre,Tamil Nadu	Approved
NIMS Institutional Ethics Committee, Hyderabad	Approved
Redkar Hospital and Research Centre Institutional Ethics Committee, Goa	Approved

Regulatory Clearance Status from DCGI
Modification(s)

Status
Approved/Obtained

Health Condition

/ Problems Studied

Health Type	Condition
Healthy Human Volunteers	Active immunization for the prevention of SARS-CoV-2 infection

Intervention / Comparator Agent
Modification(s)

Type	Name	Details
Intervention	BBV152A, BBV152B and BBV152C	Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) with three formulations, BBV152A, BBV152B and BBV152C. Dose: 0.5ml, Route of administration:Intramuscular injection, Frequency: Two doses at Day 0 and Day 14
Comparator Agent	Placebo	Placebo will be used as a control. Dose: 0.5ml Route of administration:Intramuscular injection, Frequency:Two doses at Day 0 and Day 14

Inclusion Criteria
Modification(s)

Age From	12.00 Year(s)
Age To	65.00 Year(s)
Gender	Both
Details	Phase 1 1. Ability to provide written informed consent (Audio video consent for vulnerable subjects). 2. Participants of either gender of age between ≥18 to ≤55 years. 3. Good general health as determined by the discretion of investigator (vital signs (heart rate ≥60 to≤100 bpm; blood pressure systolic ≥90 mm Hg and <140 mm Hg; diastolic ≥ 60 mm Hg and <90 mm Hg; oral temperature <100.4ºF), medical history, and physical examination). 4. Expressed interest and availability to fulfill the study requirements. 5. For a female participant of child-bearing potential, planning to avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least four weeks after the last vaccination 6. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner from first vaccination until 3 months after last vaccination 7. Male subjects agree to refrain from sperm donation from the time of first vaccination until 3 months after last vaccination 8. Participants must refrain from blood or plasma donation from the time of first vaccination until 3 months after last vaccination 9. Agrees not to participate in another clinical trial at any time during the study period. 10. Agrees to remain in the study area for the entire duration of the study. 11. Willing to allow storage and future use of biological samples for future research. Phase 2: 1. Ability to provide written informed consent (Audio video consent for vulnerable subjects). 2. Participants of either gender of age between ≥12 to ≤ 65 years. 3. Good general health as determined by the discretion of investigator (vital signs (heart rate ≥60 to≤100 bpm; blood pressure systolic ≥90 mm Hg and <140 mm Hg; diastolic ≥ 60 mm Hg and <90 mm Hg; oral temperature <100.4ºF), medical history, and physical examination). 4. Expressed interest and availability to fulfill the study requirements. 5. For a female participant of child-bearing potential, avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least four weeks after the last vaccination and agrees not to participate in another clinical trial at any time during the study period. 6. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner from first vaccination until 3 months after last vaccination 7. Male subjects agree to refrain from sperm donation from the time of first vaccination until 3 months after last vaccination 8. Participants must refrain from blood or plasma donation from the time of first vaccination until 3 months after last vaccination. 9. Agrees to remain in the study area for the entire duration of the study. 10. Willing to allow storage and future use of biological samples for future

		research.
ExclusionCriteria	**Details**	Phase 2: 1. History of any other COVID-19 investigational vaccination. 2. Unacceptable laboratory abnormality from screening (prior to first vaccination) or safety testing, as listed below [Abnormal Complete Blood Count (CBC), Random blood sugar level, Renal function test (serum urea and Creatinine), liver function tests, urine analysis report, Positive serology for hepatitis C or HIV antibody or hepatitis B surface antigen]. (Subjects will be informed if their results are positive for hepatitis C, HIV 1 & 2 antibody or hepatitis B surface antigen (HBsAg) and will be referred to a primary care provider for follow up of these abnormal laboratory tests.) 3. Confirmed SARS-CoV-2 at the time of screening using RT-PCR and/or ELISA method. 4. Health care workers. 5. For women, a positive serum pregnancy test (during screening within 45 days of enrolment) or positive urine pregnancy test (within 24 hours of administering each dose of vaccine). 6. Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine. 7. Medical problems as a result of alcohol or illicit drug use during the past 12 months. 8. Receipt of an experimental agent (vaccine, drug, device, etc.) within 60 days before enrollment or expects to receive an investigational agent during the study period. 9. Receipt of any licensed vaccine within four weeks before enrolment in this study. 10. Known sensitivity to any ingredient of the study vaccines, or a more severe allergic reaction and history of allergies in the past. 11. Receipt of immunoglobulin or other blood products within the three months prior to vaccination in this study. 12. Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months. 13. Long-term use (> 2 weeks) of oral or parenteral steroids (glucocorticoids) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding six months (nasal and topical steroids are allowed). 14. Any history of hereditary angioedema or idiopathic angioedema. 15. Any history of anaphylaxis in relation to vaccination. 16. Any history of albumin-intolerance. 17. Pregnancy, lactation, or willingness/intention to become pregnant during the study. 18. History of any cancer. 19. History of psychiatric severe conditions likely to affect participation in the study. 20. A bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder, or prior history of significant bleeding or bruising following IM injections or venepuncture. 21. Any other serious chronic illness requiring hospital specialist supervision. 22. Chronic respiratory diseases like severe acute respiratory syndrome (SARS), including mild asthma. 23. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness 24. Morbidly obese (BMI≥35 kg/m2) or underweight (BMI ≤18 kg/m2). 25. Living in the same household of any COVID-19 positive person. 26. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a volunteer participating in the trial or would render the subject unable to comply with the protocol. Re-Vaccination Exclusion Criteria 27. Pregnancy. 28. Anaphylactic reaction following administration of the investigational vaccine. 29. Virologically confirmed cases of COVID-19 Phase 2: 1. History of any other COVID-19 investigational vaccination. 2. Confirmed SARS-CoV-2 at the time of screening using RT-PCR and /or ELISA method. 3. Health care workers.

4. Positive urine pregnancy test (within 24 hours of administering each dose of vaccine).
5. Temperature > 38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine.
6. Medical problems as a result of alcohol or illicit drug use during the past 12 months.
7. Receipt of an experimental agent (vaccine, drug, device, etc.) within 60 days before enrolment or expects to receive an investigational agent during the study period.
8. Receipt of any licensed vaccine within four weeks before enrolment in this study.
9. Known sensitivity to any ingredient of the study vaccines, or a more severe allergic reaction and history of allergies in the past.
10. Receipt of immunoglobulin or other blood products within the three months prior to vaccination in this study.
11. Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months.
12. Long-term use (> 2 weeks) of oral or parenteral steroids (glucocorticoids) or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the preceding six months (nasal and topical steroids are allowed).
13. Any history of hereditary angioedema or idiopathic angioedema.
14. Any history of anaphylaxis in relation to vaccination.
15. Any history of albumin-intolerance.
16. Pregnancy, lactation, or willingness/intention to become pregnant during the study.
17. History of any cancer.
18. History of psychiatric severe conditions likely to affect participation in the study.
19. A bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder, or prior history of significant bleeding or bruising following IM injections or venepuncture.
20. Any other serious chronic illness requiring hospital specialist supervision.
21. Chronic respiratory diseases like severe acute respiratory syndrome (SARS), including mild asthma.
22. Chronic cardiovascular disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness
23. Morbidly obese (BMI≥35 kg/m2) or underweight (BMI ≤18 kg/m2).
24. Living in the same household of any COVID-19 positive person.
25. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a volunteer participating in the trial or would render the subject unable to comply with the protocol.
Re-Vaccination Exclusion Criteria
26. Pregnancy.
27. Anaphylactic reaction following administration of the investigational vaccine.
28. Virologically confirmed cases of COVID-19.

Method of Generating Random Sequence	Computer generated randomization
Method of Concealment	Centralized
Blinding/Masking	Participant, Investigator and Outcome Assessor Blinded

Primary Outcome Modification(s)

Outcome	TimePoints
Phase 1: 1. The occurrence of immediate adverse events within two hours of vaccination 2. The occurrence of adverse events within 7 days of vaccination.3. The occurrence of any adverse events throughout the study duration 4. The occurrence of serious adverse events (SAEs) Phase 2: Primary 1. To evaluate the immunogenicity in terms of GMT and four-fold	Phase 1: Occurrence of Adverse events within 2hrs, at Day 7 and through out the study duration Phase 2: Day 0, Day 14, Day

	seroconversion rate amongst the two selected BBV152 vaccine formulations | 28, Day 42 Day 104 and Day 194 in two cohorts
Secondary Outcome Modification(s)	**Outcome** | **TimePoints** Phase 1 To evaluate the immunogenicity in terms of GMT and four-fold seroconversion rate of neutralizing antibodies (NAbs) across the three formulations of BBV152 in comparison with control group. Phase 2 The occurrence of immediate adverse events within two hours of vaccination.2. The occurrence of adverse events within seven days of vaccination 3. The occurrence of any adverse events throughout the study duration 4. The occurrence of serious adverse events (SAEs). | Phase 1: Day 0, Day 14, Day 28, Day 42 Day 104 and Day 194 in two cohorts. Phase 2: Occurrence of Adverse events within 2hrs, at Day 7 and through out the study duration
Target Sample Size	**Total Sample Size=**"1125" **Sample Size from India=**"1125"
Phase of Trial	Phase 1/ Phase 2
Date of First Enrollment (India)	13/07/2020
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**"1" **Months=**"3" **Days=**"0"
Recruitment Status of Trial (Global) Modification(s)	Not Applicable
Recruitment Status of Trial (India)	Completed
Publication Details Modification(s)	NIL
Brief Summary Modification(s)	This is a phase 1 to be followed by phase 2 randomized, double-blind, multicenter study to evaluate the safety, reactogenicity, tolerability and immunogenicity of the Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) in healthy volunteers. The study is designed to evaluate the safety, reactogenicity, tolerability, and immunogenicity of three groups of healthy volunteers who receive two intramuscular doses of BBV152 vaccine formulations. A total sample size of 1125 healthy volunteers, with 375 volunteers in the phase 1 study and 750 volunteers in phase 2 study (4:1 test and control).

File No: BIO/CT/20/000159
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

From:

The Drugs Controller General, India
Directorate General of Health Services,

FDA Bhawan Kotla Road,
New Delhi-110002
Date: 23/10/2020

To

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderabad, India -500 078.

Subject: Permission for conducting a Phase III clinical trial titled " An Event-Driven, Phase 3,Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥18 Years of Age" vide Protocol No: BBIL/BBV152-C/2020 Version No: 3.0 Date: 20-10-2020.- regarding.

Reference: Your Application No. BIO/CT04/FF/2020/21960 dated 28-SEP-2020 on the subject mentioned above.

Sir,

Please refer to your application no. No. BIO/CT04/FF/2020/21960 dated 28-SEP-2020, received by this office on the above subject. Please find enclosed herewith permission to conduct clinical trial in Form CT-06 under the New Drugs and Clinical Trials Rules, 2019 along with the details of new drug and clinical trial sites.

Please acknowledge receipt of the same.

Yours faithfully,

VENUGOPAL GIRDHARILAL SOMANI

Digitally signed by VENUGOPAL GIRDHARILAL SOMANI
DN: c=IN, o=MINISTRY OF HOME AFFAIRS, ou=CDSCO DGHS, postalCode=431401, st=Maharashtra, 2.5.4.20=173d03345d862d489632379a1471bfdae9f0b2bea56c83bfbbc2154e399b1af7, cn=VENUGOPAL GIRDHARILAL SOMANI
Date: 2020.10.23 16:46:27 +05'30'

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority

File No: BIO/CT/20/000159

Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FORM CT-06
(See rules 22, 25, 26, 29 and 30)

PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licencing Authority hereby permits M/s Bharat Biotech International Limited, Genome Valley, Shameerpet (India) -500078, Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com, to conduct clinical trial of the new drug or investigational new drug as per **Protocol No.: BBIL/BBV152-C/2020 Version No: 3.0 Date: 20-10-2020** in the below mentioned clinical trial sites.

CT No.: CT- 23/2020

2. Details of new drug or investigational new drug and clinical trial site [As per Annexure].

3. This permission is subject to the conditions prescribed in part A of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

VENUGOPAL GIRDHARILAL SOMANI

Digitally signed by VENUGOPAL GIRDHARILAL SOMANI DN: c=IN, o=MINISTRY OF HOME AFFAIRS, ou=CDSCO DGHS, postalCode=431401, st=Maharashtra, 2.5.4.20=173d03345df62d489632375a1471bfdae9f9b2bea56c83bfbbe2154e399b1af7, cn=VENUGOPAL GIRDHARILAL SOMANI Date: 2020.10.23 16:48:12 +05'30'

Place: New Delhi
Date: 23/10/2020

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority
Stamp

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

Annexure:

Details of New Drug or Investigational New Drug:

Name of the new drug or investigational new drug:	Whole Virion Inactivated Corona Virus Vaccine, [BBV152B]	
Therapeutic class:	Vaccine	
Dosage form:	Liquid for intramuscular injection	
Composition:	Each dose of 0.5 ml contains	
	Active ingredient	**Quantity**
	Whole Virion, Inactivated Corona Virus antigenStrain: NIV-2020-770	6 mcg
	Inactive ingredients	
	Aluminium Hydroxide gel equivalent to Al+++	250 mcg
	TLR 7/8 Agonist	15 mcg
	2-Phenoxyethanol (2PE) I.P.	2.5 mg
	Phosphate Buffered Saline	Qs to 0.5 ml
Indications:	For active immunization against Corona Virus Disease(SARS-COV-2) COVID-19	

Details of clinical trial sites-

S. No.	Name and Address of Clinical Trial Site	Ethics Committee details	Name of Principal Investigator
1	Institute of Medical Sciences (IMS) & SUM Hospital, K 8, Kalinga Nagar, Ghatikia, Bhubaneshwar -751003, Odisha	Institutional Ethics Committee, IMS & SUM Hospital, K 8, Kalinga Nagar, Ghatikia, Bhubaneshwar 751003, Odisha ECR/627/Inst/OR/2014/RR-20	Dr. E. Venkata Rao
2	Guwahati institute of medical sciences Bhangagarh, Kamrup, Assam - 781032	State Cancer Institute Ethics Committee Bhangagarh, Guwahati-781032 ECR/1289/Inst/AS/2019	Dr. Anjan Jyoti Talukdar
3	Lokmanya Tilak Municipal Medical College & General Hospital, Dr. Ambedkar Road, Sion, Mumbai 400022	Institutional Ethics Committee Lokmanya Tilak Municipal Medical College & General Hospital, Dr. Ambedkar Road, Sion, Mumbai 400022 ECR/266/Lokamanya/Inst/MH2013/RR-19	Dr. N.T. Awad
4	Nizam's institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, 500082	NIMS Institutional Ethics Committee, Nizam's institute of Medical Sciences, Punjagutta, Hyderabad , Telangana, 500082	Dr Prabhakar Reddy
5	Vagus Super Specialty Hospital, #18th Cross, Margosa Road, Malleshwaram, Bangalore - 560003	Vagus Institutional Ethics Committee, 1 8thCross Rd, Margosa Road, Malleshwaram West, Bengaluru, Karnataka 560003	Dr. Meghana Murthy

6	UCMS & GTB Hospital, Dilshad Garden Delhi 110095	Institutional Ethics Committee, UCMS & GTB Hospital, Dilshad Garden Delhi 110095 ECR/510/Inst/DL/2014/RR-20	Dr. Shiva Narang
7	Rahate Surgical Hospital & ICU, near telephone exchange square, 517, Juni Mangalwari, Central Avenue, Nagpur 440008	Ethics Committee Rahate Surgical Hospital & ICU, near telephone exchange square, 517, Juni Mangalwari, Central Avenue, Nagpur 440008	Dr Manish Kishore Multani
8	ESIC Medical College and Hospital NH-3, behind BK Hospital, New Industrial Town, Faridabad, Haryana 121012	Ethics Committee ESIC Medical College and HospitalNH-3, behind BK Hospital,New Industrial Town, Faridabad, Haryana 121012	Dr Anil Kumar Pandey
9	All India Institute of Medical Sciences, Ansari Nagar New Delhi India 110029	Ethics Committee All India Institute of Medical Sciences, Ansari Nagar New Delhi India 110029	Dr Sanjay Kumar Rai
10	Grant Government Medical College and Sir J.J. Group of Hospitals. J J Marg, Nagpada, Mumbai Central, Mumbai, Maharashtra 400008	Grant Government Medical College and Sir J.J. Group of Hospitals. J J Marg, Nagpada, Mumbai Central, Mumbai, Maharashtra 400008	Dr Priti Meshram
11	Prince Aly Khan Hospital, Jamatkhana uilding, Nesbit Rd, Tara Bagh, Mazagon, Mumbai, Maharashtra 400010	Ethics Committee Prince Aly Khan Hospital, Jamatkhana Building, Nesbit Rd, Tara Bagh, Mazagon, Mumbai, Maharashtra 400010	Dr. Tapan Kumar Saikia
12	All India Institute of Medical Sciences, Aurangabad Road Phulwari Sharif Patna Bihar-801507	Ethics Committee All India Institute of Medical Sciences, Aurangabad Road Phulwari Sharif Patna Bihar-801507	Dr Chadramani Singh
13	Baba Raghav Das Medical College, Gorakhpur, Uttar Pradesh 273013	Ethics Committee Baba Raghav Das Medical College, Gorakhpur, Uttar Pradesh 273013	Dr Azhar Ali Khan
14	Mahatma Gandhi Medical College& Research Institute, Pondicherry- Cuddalore, ECR Main Road, Pillayarkuppam 607-402, Pondicherry, India	Ethics Committee Mahatma Gandhi Medical College& Research Institute, Pondicherry- Cuddalore, ECR Main Road, Pillayarkuppam 607-402, Pondicherry, India	Dr. Pajanivel Ranganadin
15	Vydehi Institute of Medical Sciences and Research Centre 82, near BMTC 18th Depot, Vijayanagar, Nallurhalli, Whitefield, Bengaluru, Karnataka 560066	Ethics Committee Vydehi Institute of Medical Sciences and Research Centre 82, near BMTC 18th Depot, Vijayanagar, Nallurhalli, Whitefield, Bengaluru, Karnataka 560066	Dr Akshata
16	King George Hospital, KGH Down Rd, Opp KGH OP Gate, Maharani Peta, Visakhapatnam, Andhra Pradesh 531011	Ethics Committee King George Hospital , Opp KGH OP Gate, Maharani Peta, Visakhapatnam, Andhra Pradesh 531011	Dr R Vasudev
17	People's university Ayodhya Bypass Rd, Peoples Campus, Bhanpur, Bhopal, Madhya Pradesh 462037	Ethics Committee People's university Ayodhya Bypass Rd, Peoples Campus, Bhanpur, Bhopal, Madhya Pradesh 462037	Dr Raghavendra Gumashta

18	Gandhi Medical College Sultania Rd, near Hamidia Hospital, Royal Market, Medical College Campus, Kohefiza, Bhopal, Madhya Pradesh 462001	Ethics Committee Gandhi Medical College Sultania Rd, near Hamidia Hospital, Royal Market, Medical College Campus, Kohefiza, Bhopal, Madhya Pradesh 462001	Dr Simmi Dube
19	Pt BD Sharma,PGIMS/UHS. Rohtak, Haryana	Ethics Committee Pt BD Sharma,PGIMS/UHS.Rohtak, Haryana	Dr Savita Verma
20	Redkar Hospital and Research Centre Oshalbag Village Dhargal, Tal- Pernem. Goa- 403513, India	Ethics Committee Redkar Hospital and Research Centre Oshalbag Village Dhargal, Tal- Pernem. Goa-403513, India	Dr. Sagar Vivek Redkar
21	Guntur Medical College, Government Fever Hospital, Government General Hospital, Gorantla, Guntur - 5220020	Ethics Committee, Guntur Medical College, Government Fever Hospital, Government General Hospital, Gorantla, Guntur - 5220020	Dr Laxmi S Kumari

In addition to point 3, the permission is subject to following condition(s):

I. The Phase III clinical trial should be conducted as per protocol titled "An Event-Driven, Phase 3,Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥18 Years of Age" vide Protocol No: BBIL/BBV152-C/2020 Version No: 3.0 Date: 20-10-2020.

II. The formulation intended to be used in the clinical trial shall be manufactured under GMP conditions using validated procedures and shall have ongoing stability programme.

III. Only CDL, Kasauli certified batches shall be used in the clinical trial.

VENUGOPAL
GIRDHARILAL
SOMANI

Digitally signed by VENUGOPAL GIRDHARILAL SOMANI
DN: c=IN, o=MINISTRY OF HOME AFFAIRS, ou=CDSCO DGHS, postalCode=431401, st=Maharashtra, 2.5.4.20=173d03345df62d4896323792147 1b1dae9f0b2bea56c83bfbbe2154e399b1af7, cn=VENUGOPAL GIRDHARILAL SOMANI
Date: 2020.10.23 16:48:39 +05'30'

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licencing Authority
Stamp

Place: New Delhi
Date: 23/10/2020

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

FULL DETAILS (Read-only)

CTRI Number	**CTRI/2020/11/028976** [Registered on: 09/11/2020] **Trial Registered Prospectively**
Last Modified On:	17/03/2021
Post Graduate Thesis	No
Type of Trial	Interventional
Type of Study	Vaccine
Study Design	Other
Public Title of Study Modification(s)	A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole virion Inactivated Vaccine in Adults greater than or equal to 18 Years of Age.
Scientific Title of Study Modification(s)	An Event-Driven,Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity,and Lot-to-Lot consistency of BBV152, a Whole virion Inactivated SARS-CoV-2 Vaccine in Adults greater than or equal to 18 Years of Age.
Secondary IDs if Any	**Secondary ID** / **Registry** BBIL/BBV152-C/2020 Version No: 3.0; Date: 20-10-2020 / Protocol Number
Details of Principal Investigator or overall Trial Coordinator (multi-center study)	**Name**: Dr Krishna Mohan **Address**: Medical Affairs Department, Bharat Biotech International Ltd, Genome valley, Shameerpet Medchal TELANGANA 500078 India **Phone**: 914023480567 **Fax**: 914023480560 **Email**: kmohan@bharatbiotech.com
Details Contact Person Scientific Query	Name: Dr Krishna Mohan **Address**: Medical Affairs Department, Bharat Biotech International Ltd, Genome valley, Shameerpet Medchal TELANGANA 500078 India **Phone**: 914023480567 **Fax**: 914023480560 **Email**: kmohan@bharatbiotech.com
Details Contact Person Public Query	**Name**: Dr Shashikanth Muni **Address**: Medical Affairs Department, Bharat Biotech International Ltd, Genome valley, Shameerpet Medchal TELANGANA 500078 India **Phone**: 914023480567 **Fax**: 914023480560 **Email**: shashikanth4257@bharatbiotech.com
Source of Monetary or Material Support	Indian Council of Medical Research (ICMR), New Delhi
Primary Sponsor	**Name**: Bharat Biotech International Ltd **Address**: Bharat Biotech International Ltd Genome Valley Shameerpet Hyderabad – 500 078 Telagana INDIA

Type of Sponsor	Pharmaceutical industry-Indian

Details of Secondary Sponsor

Name	Address
The Indian Council of Medical Research ICMR New Delhi	Indian Council of Medical Research V. Ramalingaswami Bhawan, P.O. Box No. 4911 Ansari Nagar, New Delhi - 110029, India

Countries of Recruitment

India

Sites of Study
Modification(s)

No of Sites = **26**

Contact Person	Name of Site	Site Address	Phone/Fax/Email
Dr Mohammad Shameem	Aligarh Muslim University	Department of Tuberculosis and respiratory diseases, Professor Interventional Pulmonology Aligarh, Uttar Pradesh 202001 Aligarh	9412731835 mshameem@myamu.ac.in
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Dr Priti Meshram	Grant Government Medical College and	Grant Government Medical College and Sir J.J. Group of Hospitals.	9323198298 drpritimeshram@gmail.com

	Sir J.J. Group of Hospitals	J J Marg, Nagpada, Mumbai Central, Mumbai, Maharashtra 400008 Mumbai	
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Dr Pajanivel Ranganadin	Mahatma Gandhi Medical College& Research Institute	Mahatma Gandhi Medical College& Research Institute, Pondicherry-Cuddalore, ECRMain Road, Pillayarkuppam 607-402, Pondicherrv, India Pondicherry	9443493122 pajanivelr@mgmcri.ac.in
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		Clinical Pharmacology & Therapeutics, (CP&T),Hyderabad Hyderabad	
Dr Raghavendra Gumashta	Peoples College Of Medical Sciences & Research Centre And Associated People's Hospital	Peoples College Of Medical Sciences & Research Centre And Associated People's Hospital, Peoples Campus, Bhanpur, Bhopal, Madhya Pradesh 462037 Bhopal	9425324588 rgumashta@gmail.com
Dr VijayKumar Shivajirao patil	Prakash Institute of Medical Science and Technology	Medical Superintendent 2nd floor Islampur Sangli Road Tal-Walwa Sangli	9371877555 prakashmc.research@gmail.com
Dr Jitendra SIngh Kushwaha	Prakhar Hospital	8/219 Khalasi Line Arya Nagar 3rd floor Kanpur Uttar Prasedh Kanpur Nagar	08448522450 dr.jskushwahacr@gmail.com
Dr Savita Verma	Pt BD Sharma,PGIMS/UHS. Rohtak, Haryana	PGIMS Room no428 Department of Pharmacology Directorate Office of Rohtak Pt BD SHARMA,PGIMS/UHS. Rohtak, HARYANA Rohtak	9812283746 verma.savi@gmail.com
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Dr Sunita Jaiprakash Ramanand	RCSMGMC & CPR Hospital	Professor and HOD of Pharmacological Department Dasara Chowk Town Hall Bhausingji Road Kolhapur Kolhapur	8080328480 rcsmgmc.research@gmail.com
Dr Sagar Vivek Redkar	Redkar Hospital and Research Centre	Redkar Hospital and Research Centre Consultant Physician Room No. 11, Mumbai Goa Highway, Oshalbag Village Dhargal, Tal- Pernem. Goa- 403513, India North Goa	09146885522 drsagarredkar@gmail.com
Dr Anupam Sachdeva	Sir Ganga Ram Hospital	Sir Ganga Ram Hospital (SGRH), New Delhi-110060, INDIA. New Delhi	9811043476 anupamace@yahoo.co.in
Dr Satyajit Mohapatra	SRM Hospital & Research center	Department of Pharmacology , SRM Medical College Hospital and Research Centre, Kattankulathur Campus Kancheepuram	09791161626 satyajitmp@gmail.com

Dr Akshata	Vydehi Institute of Medical Sciences and Research Centre	Vydehi Institute of Medical Sciences and Research Centre 82, near BMTC 181h Depot, Vijayanagar, Nallurhalli, Whitefield, Bengaluru, Karnataka 560066 Bangalore	9845244541 dr_akshata@yahoo.co.in

Details of Ethics Committee Modification(s)

No of Ethics Committees= **26**

Name of Committee	Approval Status
Ethics Committee of the Prakhar Hospital	Approved
Ethics Committee Sir Ganga Ram Hospital	Approved
Institutional Ethics Committe Aligarh Muslim University UP	Approved
Institutional Ethics Committe, Jeevan Rekha Hospital, belgaum	Approved
Institutional Ethics Committe, Maharaja Agrasen Superspecilaity Hospital, Jaipur	Approved
Institutional Ethics Committee SRM College Hospital and Research Centre Tamil Nadu	Approved
Institutional Ethics Committee All India Institute of Medical Sciences Bihar	Approved
Institutional Ethics Committee All India Institute of Medical Sciences New Delhi	Approved
Institutional ethics committee DIRECTORATE OF PUBLIC HEALTH AND PREVENTIVE MEDICINE,Chennai	Approved
Institutional ethics committee Gmers Ahmedabad	Approved
Institutional Ethics Committee Grant Government Medical College and Sir J.J. Group of Hospitals Maharashtra	Approved
Institutional ethics committee ICMR-National Institute of Cholera and Enteric Diseases Kolkatta,West Bengal	Approved
Institutional Ethics Committee King George Hospital Visakhapatnam	Approved
Institutional Ethics Committee Lokmanya Tilak Municipal Medical College & General Hospital	Approved
Institutional Ethics Committee Mahatma Gandhi Medical College& Research Institute, Pondicherry	Approved
Institutional Ethics Committee Peoples university Bhopal, Madhya Pradesh	Approved
Institutional Ethics Committee Pt BD Sharma,PGIMS/UHS.Rohtak, Harvana	Approved
Institutional Ethics Committee Rahate Surgical Hospital & ICU Nagpur	Approved
Institutional Ethics Committee Redkar Hospital and Research Centre Oshalbag Village Dhargal, Tai- Pernem. Goa	Approved
Institutional Ethics Committee Vydehi Institute of Medical Sciences and Research Centre Bengaluru, Karnataka	Approved
Institutional Ethics Committee, Guntur Medical College, Government Fever Hospital, Government General Hospital, Gorantla, Guntur	Approved
Institutional Ethics Committee, IMS & SUM Hospital	Approved
NIMS Institutional Ethics Committee, Nizams institute of Medical Sciences, Punjagutta,	Approved
Prakash Medical college Institutional Ethics Committee	Approved
RCSMGMCIEC	Approved
Translational Health Science and Technology Institute(THSTI), ESIC Medical College and Hospital Faridabad	Approved

Regulatory Clearance Status from DCGI

Status
Approved/Obtained

Health Condition / Problems Studied

Health Type	Condition
Healthy Human Volunteers	Active immunization for the prevention of SARS-CoV-2 infection

Intervention / Comparator Agent

Type	Name	Details
Intervention	BBV152B: 6 µg antigen with Algel-IMDG	Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152) will be administered as a two dose intramuscular injection 28 days apart.

	Comparator Agent	Placebo (Phosphate buffered saline with Algel)	Phosphate buffered saline with Alum (without antigen) will be used as the control.will be administered as a two dose intramuscular injection 28 days apart.

Inclusion Criteria	**Age From**	18.00 Year(s)
	Age To	99.00 Year(s)
	Gender	Both
	Details	1. Ability to provide written informed consent and availability to fulfill the study requirements. 2. Participants of either gender of aged 18 years and above. 3. Participants with good general health as determined by the discretion of the investigator, or participants with stable medical conditions. A stable medical condition is defined as a disease not requiring significant change in therapy or hospitalization or worsening disease during the 3 months before enrolment. 4. For a female participant of child-bearing potential, planning to avoid becoming pregnant (use of an effective method of contraception or abstinence) from the time of study enrolment until at least eight weeks after the last vaccination. 5. Male subjects of reproductive potential: Use of condoms to ensure effective contraception with the female partner and to refrain from sperm donation from first vaccination until at least 3 months after the last vaccination. 6. Agrees not to participate in another clinical trial at any time during the study period. 7. Agrees not to take any COVID-19 licensed vaccination for the entire duration of the study. 8. Agrees to remain in the study area for the entire duration of the study. 9. Willing to allow storage and future use of biological samples for future research.

ExclusionCriteria	**Details**	1. History of any other COVID-19 investigational or licensed vaccination. 2. Known history of SARS-CoV-2 infection, as declared by the subject. 3. For women, positive urine pregnancy test before the first dose of vaccination, or any time during the study period. 4. Temperature >38.0°C (100.4°F) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within three days prior to each dose of vaccine. 5. Resident of COVID-19 infection in same household. 6. Known case of HIV, hepatitis B, or hepatitis C infection. 7. Receipt of any licensed/experimental vaccine within four weeks before enrolment in this study. 8. Receipt of immunoglobulin or other blood products within the three months before vaccination in this study. 9. Immunosuppression as a result of an underlying illness or treatment with immunosuppressive or cytotoxic drugs, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months. 10. Immunoglobulins, anti-cytokine antibodies and blood products within 6 months prior to study vaccination, during and 21 days following last dose of vaccination. 11. Pregnancy, lactation, or willingness/intention to become pregnant during the first 6 months after enrolment. 12. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder,, and neurological illness (mild/moderate well-controlled comorbidities are allowed) Re-Vaccination Exclusion Criteria 13. Pregnancy. 14. History of virologically (RT-PCR) confirmed SARS-CoV-2 infection 15. Anaphylactic reaction following administration of the investigational vaccine.

Method of Generating Random Sequence	Computer generated randomization
Method of Concealment	Centralized
Blinding/Masking	Participant, Investigator and Outcome Assessor Blinded

Primary Outcome	**Outcome**	**TimePoints**
	To evaluate the efficacy of BBV152B to prevent symptomatic COVID-19(Virologically confirmed-(RT-PCR positive) which include any participant who meets the Case Definitions for Symptomatic Endpoint and Severe Symptomatic COVID-19	Day 42 to Month 12

Secondary Outcome	**Outcome**	**TimePoints**
	EFFICACY:To evaluate the efficacy of BBV152B to prevent- 1. COVID-19 based on the case definition for the secondary efficacy symptomatic endpoint. 2.COVID-19-Virologically confirmed (RT-PCR positive) severe cases of COVID19. 3.Any severity of COVID-19 by age. 4.Asymptomatic COVID-19.	1.Day 42 to Month 12 2.Day 42 to Month 12. 3.Day 42 to Month 12 4.Month 2 to Month 12 5.Day 42 to Month 12 6.Day 42 to Month 12 7.Day 42 to Month 12

	5.COVID-19 regardless of symptomatology or severity 6.COVID-19 related deaths 7.Symptomatic COVID-19, regardless of the previous infection	
	IMMUNOGENECITY To evaluate the immunogenicity of BBV152B 1.Geometric Mean Titer (GMT) of SARS-CoV-2 Specific Neutralizing Antibody (nAb) 2.Geometric Mean Fold Rise (GMFR) of SARS-CoV-2 Neutralizing Antibody (nAb). 3.Geometric Mean Titer (GMT) of SARS-CoV-2 S1 protein-specific Binding Antibody (bAb). 4.Lot-to-Lot consistency will be assessed based on the neutralizing titer of the three consistent lots used in the trial	1.Month 0 to Month 12 2.Month 0 to Month 12 3.Month 0 to Month 12 4.Month 0 to Month 2
	SAFETY To assess the safety of BBV152B 1.Serious Adverse Events occurring at any time 2.Solicited local and systemic adverse events (AEs). 3.Unsolicited AEs occurring between the vaccination and 28 days after the final vaccination. 4.Immediate AEs with 30 minutes of vaccination 5. Medically attended adverse events (MAAEs) or AEs leading to withdrawal 6.The occurrence of enhanced respiratory disease episodes reported by participant/documented in hospital records 7.AE of Special interest	1.Throughout the study period 2.Within 7 days post each vaccination 3.Till 28 days post second dose vaccination 4. Within 30 minutes post each vaccination 5.Throughout the study period 6.Throughout the study period 7.Throughout the study period

Target Sample Size	**Total Sample Size=**"25800" **Sample Size from India=**"25800"
Phase of Trial	Phase 3
Date of First Enrollment (India) Modification(s)	11/11/2020
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**"1" **Months=**"0" **Days=**"0"
Recruitment Status of Trial (Global) Modification(s)	Not Applicable
Recruitment Status of Trial (India)	Closed to Recruitment of Participants
Publication Details	NIL
Brief Summary	This is a phase 3 Event Driven, randomized, double-blind, placebo controlled ,multicentre study to evaluate the Efficacy, Safety, and Immunogenicity of BBV152B, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above. Protocol Version 1.0 to Version 2.0 · BBV-152B formulation is chosen based on the Phase 1 interim report which shows that the immunogenicity of BBV-152B is higher compared to BBV-152A although the difference was not statistically different. · The primary efficacy endpoint is modified to include the participants who meet the case definition for Severe symptomatic COVID-19 . · A safety endpoint to include the Adverse Events of Special Interest (AESIs) such as anaphylaxis, generalized convulsion, and vaccine associated enhanced respiratory disease (VAERD) is included. Protocol Version 2.0 to version 3.0 · The case definition of symptomatic COVID-19 Endpoint is modified based on the SEC recommendation.

·

Risks from study participation (Category 1 and Category 2 &3) is Updated for easy understanding for the participant

A total of 25,800 subjects will be enrolled and randomized in a 1:1 ratio to receive BBV152B vaccine and control. All participants will be assessed for efficacy and safety endpoints and provide a NP swab and blood sample before the first dose of IP. The NP swab and blood collected will be subject to RT-PCR and Anti-SARS-CoV-2 IgG antibodies. The results of this will not affect enrollment of the participant. Participants who are found to be positive for either RT-PCR Or Anti-SARS-CoV-2 IgG antibodies will be excluded from the primary efficacy analysis. Safety follow up will be done for all.
In addition, sites will be segregated based on the study objectivies:
Category 1 (Symptomatic): In addition to administering the IP, a series of post-dose telephonic follow-up visits will be scheduled to detect suspect symptomatic COVID-19 infections. If a suspect is identified, a nasopharyngeal sample will be collected from the participant for detecting the presence of COVID-19 infection. Telephonic follow-up will occur at 15 Day intervals.
Category 2 (Symptomatic/Asymptomatic): In addition to administering the IP, a series of post-dose Nasopharyngeal samples for detecting incidence of asymptomatic COVID-19 infection at 1-Month intervals will be collected
Category 3 (Symptomatic/Asymptomatic+Immunogenicity): In addition to administering the IP and collecting NP samples, a series of blood samples will be collected for analyzing serum for immunological assessments.
The purpose of this Phase 3 study is to evaluate the protective efficacy, safety, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine, BBV152B. The Phase 3 study will follow randomized study participants for efficacy until virologically confirmed (RT-PCR positive) symptomatic COVID-19 participants will be eligible for the primary efficacy analysis. After reaching the target number (n=130) of symptomatic COVID-19 cases, the study will continue to assess safety until the completion of the study duration.It is planned to continue the Phase 3 trial until 130 study participants in the per-protocol population develop PCR-confirmed symptomatic COVID-19 disease during follow-up beginning 14 days after the second dose of vaccine or placebo. We estimate that approximately 25,800 participants should be randomized to accrue these 130 events. The Lot-to-Lot consistency (Immunogenicity) study will be nested within the Phase 3 (Efficacy) study (in three selected sites). The Immunogenicity study will assess the immune response of a 2-dose regimen of BBV152B vaccine through geometric mean titers (GMTs) by neutralizing antibody, S-protein, and RBD specific anti-IgG binding titer in a subset of 600 (450 vaccine: 150 control) participants, across three consecutive manufacturing Lots. Data generated through Day 56 (Month 2) will be unblinded only to the biostatistician for evaluation of immune responses in the Immunogenicity subset. A Formal interim analyses are planned when approximately 1/3 and 2/3 of the target number of participants with confirmed symptomatic COVID-19 have been accrued, to determine whether the sample size and/or length of follow-up should be increased .This interim report containing safety and immunogenicity data will be submitted to CDSCO.

ANNEXURE R/7

F. No.: BIO/MA/20/000102
Permission no.: MF/BIO/21/000001 dated 03-JAN-2021

FORM CT-23
(See rules 81, 82, 83 and 84)

PERMISSION TO MANUFACTURE PHARMACEUTICAL FORMULATION OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licensing Authority hereby grant permission to M/s Serum Institute of India Pvt. Ltd. 212/2, Off. Soli Poonawalla Road, Hadapsar Pune, Maharashtra (India) - 411028 Telephone No.: 020-26602113, 26602378, 26602978 Fax: 020-26993945, 26993921 to manufacture for sale of pharmaceutical formulation manufactured by a manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this license:

S. No	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site).
1.	M/s. Serum Institute of India Pvt. Ltd. 212/2, Off. Soli Poonawalla Road Hadapsar Pune, Maharashtra (India) – 411 028. Tel. No: +91-20-26993900, 26992113 Fax No: +91-20-26993921, Email: ssj@seruminstitute.com	M/s. Serum Institute of India Pvt. Ltd. 212/2, Off. Soli Poonawalla Road, Hadapsar Pune, Maharashtra (India) – 411 028.

Component	Manufacturing facility
Drug substance	• Bld.14, EOU, • SEZ-6, First Floor • SEZ-7, Second Floor
Drug Product	SEZ-5 Ground Floor

3. Details of pharmaceutical formulation:

Name of the New drug to be manufactured:	ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)
Dosage form:	Solution for injection Presentation: Multi-dose Glass vial (10 dose- 5ml) Route of Administration: Intramuscular
Composition:	Each dose of 0.5ml of vaccine contains:

Active Ingredients	**Quantity**
Replication- deficient chimpanzee adeno virus particles encoding SARS-CoV-2 spike (S) glycoprotein*	5×10^{10} virus particles
Inactive Ingredients	**Quantity**
L-Histidine and L-Histidine Hydrochloride	10 mM
Sodium Chloride	35 mM
Magnesium Chloride	1 mM
Polysorbate 80	0.1% (w/v)
Sucrose	7.5% (w/v)
Ethanol	0.5% (w/v)
EDTA Disodium Salt	0.1 mM
Water for Injection	q.s. to 0.5 ml

* Produced in genetically human embryonic kidney (HEK) 293 cells.

Indication:	For active immunization of individuals of ≥18 years old for the prevention of corona virus disease (COVID-19) when administered in two doses schedule. The second dose should be administered between 4 to 6 weeks after the first dose. However, there is data available for administration of the second dose up to 12 weeks after the first dose from the overseas studies.
Shelf life with storage condition:	6 months when stored at 2 to 8 °C. Once opened, multi-dose vials should be used as soon as possible and within 6 hours when kept between 2 to 8°C.

4. This is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act,1940.
5. This permission is for restricted use in emergency situation for COVID-19 subject to various regulatory provisions.
6. Vaccine to be supplied for immunization programme.
7. The vaccine should be supplied along with Factsheet for recipients and prescribing information/ Package Insert (PI).
8. The firm should provide the updated Package Insert, Summary of Product Characteristics (SmPC) & Factsheet for ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) incorporating the changes as per the Subject Expert Committee (SEC) recommendations dated 01.01.2021.
9. The firm should ensure that factsheet for the vaccine recipient/his attendant is provided prior to the administration of vaccine.
10. The firm should disseminate the instructions & educational material including factsheet, PI, SmPC, storage instructions etc. through their website prior marketing/supplies of the product.
11. The firm should submit safety, efficacy & immunogenicity data from the ongoing clinical trials nationally and internationally till the completion of trial.
12. The firm should submit safety data including the data on AEFI and AESI, with due analysis, every 15 days for the first two months & monthly thereafter till the completion of the ongoing clinical trial in the country. Thereafter, the firm should submit the safety data as per the provisions and Rules.
13. The firm should provide and implement India specific Risk Management Plan.
14. The firm should submit ongoing stability (real time and accelerated) of drug substance & drug product.
15. Each batch/lot of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) shall be released from Central Drugs Laboratory, Kasauli.

VENUGOPAL GIRDHARILAL SOMANI

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

Place: New Delhi
Date: 03-Jan-2021

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

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Summary

Background A safe and efficacious vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), if deployed with high coverage, could contribute to the control of the COVID-19 pandemic. We evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four trials.

Methods This analysis includes data from four ongoing blinded, randomised, controlled trials done across the UK, Brazil, and South Africa. Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline). Participants in the ChAdOx1 nCoV-19 group received two doses containing 5×10^{10} viral particles (standard dose; SD/SD cohort); a subset in the UK trial received a half dose as their first dose (low dose) and a standard dose as their second dose (LD/SD cohort). The primary efficacy analysis included symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. Participants were analysed according to treatment received, with data cutoff on Nov 4, 2020. Vaccine efficacy was calculated as 1 – relative risk derived from a robust Poisson regression model adjusted for age. Studies are registered at ISRCTN89951424 and ClinicalTrials.gov, NCT04324606, NCT04400838, and NCT04444674.

Findings Between April 23 and Nov 4, 2020, 23 848 participants were enrolled and 11 636 participants (7548 in the UK, 4088 in Brazil) were included in the interim primary efficacy analysis. In participants who received two standard doses, vaccine efficacy was 62·1% (95% CI 41·0–75·7; 27 [0·6%] of 4440 in the ChAdOx1 nCoV-19 group *vs* 71 [1·6%] of 4455 in the control group) and in participants who received a low dose followed by a standard dose, efficacy was 90·0% (67·4–97·0; three [0·2%] of 1367 *vs* 30 [2·2%] of 1374; $p_{interaction}$=0·010). Overall vaccine efficacy across both groups was 70·4% (95·8% CI 54·8–80·6; 30 [0·5%] of 5807 *vs* 101 [1·7%] of 5829). From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were 74 341 person-months of safety follow-up (median 3·4 months, IQR 1·3–4·8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events were classified as possibly related to a vaccine: one in the ChAdOx1 nCoV-19 group, one in the control group, and one in a participant who remains masked to group allocation.

Interpretation ChAdOx1 nCoV-19 has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19 in this interim analysis of ongoing clinical trials.

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Research in context

Evidence before this study

We searched PubMed for research articles published from database inception until Nov 23, 2020, with no language restrictions, using the terms "SARS-CoV-2", "vaccine", "clinical trial", and "efficacy". There were no peer-reviewed publications available on efficacy of any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in development and, at the time of the search, there were no licensed vaccines against SARS-CoV-2. Three vaccine developers recently reported initial efficacy results from phase 3 trials in the media (Pfizer/BioNTech, Moderna, and the Gamaleya National Research Center). Pfizer/BioNTech and Moderna, both developing mRNA vaccines, have reported initial efficacy results of 95% in their primary analysis (Pfizer/BioNTech) and 94·5% in an interim analysis (Moderna). We have previously published safety and immunogenicity results of ChAdOx1 nCoV-19 (AZD1222) for different age groups in phase 1/2 and 2/3 trials.

Added value of this study

We report on the first clinical efficacy results of ChAdOx1 nCoV-19 in a pooled analysis of phase 2/3 trials in the UK and Brazil, and safety data from more than 20 000 participants enrolled across four clinical trials in the UK, Brazil, and South Africa. ChAdOx1 nCoV-19 has an acceptable safety profile and is efficacious against symptomatic COVID-19, with no hospital admissions or severe cases reported in the ChAdOx1 nCoV-19 arm. The vaccine can be stored and distributed at 2–8°C, making it particularly suitable for global distribution.

Implications of all the available evidence

The development of safe, effective, affordable, and deployable vaccines against COVID-19 remains paramount in solving the pandemic crisis and re-establishing normality. The positive results presented here support regulatory submissions for conditional or emergency use of ChAdOx1 nCoV-19.

Introduction

As the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to unfold, there has been widespread impact on health, including substantial mortality among older adults and those with pre-existing health conditions,[1,2] and repercussions for the global economy, caused by physical distancing measures, with the greatest consequences for the most vulnerable in society.

Despite global spread of the virus, a large proportion of the population in many countries is thought to have thus far escaped infection and remains non-immune to SARS-CoV-2.[3] Vaccines could play an important role in increasing population immunity, preventing severe disease, and reducing the ongoing health crisis. In response, rapid global efforts to develop and test vaccines against SARS-CoV-2 have led to an unprecedented number of candidate vaccines starting clinical trials during 2020. Currently, 48 vaccines are under clinical evaluation.[4] Several of these have shown good safety and immunogenicity, and 11 of these are currently being evaluated in phase 3 clinical efficacy studies.

The ChAdOx1 nCoV-19 vaccine (AZD1222) was developed at Oxford University and consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene.

Following initiation of a phase 1 clinical trial in the UK (COV001) on April 23, 2020, three further randomised controlled trials of the candidate vaccine were initiated across the UK (COV002), Brazil (COV003), and South Africa (COV005). A further phase 1/2 trial has recently been initiated in Kenya and is not reported here. The immunogenicity results from the phase 1/2 UK study, COV001, in 1077 healthy adults aged 18–55 years,[5] and a phase 2 cohort in COV002 in older adults (≥56 years)[6] have been published and show an acceptable safety profile for the vaccine with induction of binding and neutralising antibodies as well as generation of interferon-γ enzyme-linked immunospot responses, with higher antibody titres after a second dose of vaccine.[5–7]

The phase 1 study (COV001) included an efficacy cohort and the phase 2 and 3 studies (COV002, COV003, and COV005) expanded enrolment to a wider population of participants with higher likelihood of exposure to the virus, such as health-care workers. Exclusion criteria were reduced for phase 3 trials, so that older adults and individuals with a range of comorbidities were also enrolled.

All studies have completed enrolment of their respective efficacy cohorts and are in the follow-up phase. Paediatric studies have not yet been initiated.

Here, we present the combined interim analysis of efficacy and safety from randomised controlled trials of ChAdOx1 nCoV-19.

Methods

Overview

This interim analysis of the efficacy and safety of the ChAdOx1 nCoV-19 vaccine includes data from four ongoing blinded, randomised, controlled trials done across three countries: COV001 (phase 1/2; UK), COV002 (phase 2/3; UK), COV003 (phase 3; Brazil), and COV005 (phase 1/2; South Africa). The interim efficacy is being assessed by a prespecified global pooled analysis combining data from COV002 and COV003. The safety of the vaccine is being assessed using data from all four studies (appendix 1 pp 3–4). Three of the studies are single blind and one is double blind (COV005). Primary efficacy was assessed in participants who received

two doses of the vaccine. All four studies included participants who received two doses, with a booster dose incorporated into the three trials[6] that were initially designed to assess a single-dose of ChAdOx1 nCoV-19 compared with control (COV001, COV002, and COV003) after review of the antibody response data from COV001.

Despite minor differences across the studies, there is sufficient consistency to justify the proposal for pooled analysis of data, which will provide greater precision for both efficacy and safety outcomes than can be achieved in individual studies and provides a broader understanding of the use of the vaccine in different populations. Once the studies were underway, a statistical analysis plan for the global pooled analysis of these studies was developed before data lock on Nov 4, 2020, and analysis, and was finalised with extensive feedback from national and international regulators (including the Medicines and Healthcare Products Regulatory Agency [UK] and the European Medicines Agency [EU]), including justification for including groups receiving different vaccine doses in the analysis (see statistical analysis plan for further details; appendix 2 pp 2–73). All participants in the four trials provided written informed consent.

Details of amendments to the four trial protocols and the statistical analysis plan are included in appendix 2 (pp 9, 178–182, 327–335, 438–441, 548–550).

Study design and participants

COV001 (UK)

COV001 is a continuing single-blind phase 1/2 clinical trial in five sites in the UK, which began on April 23, 2020, and enrolled 1077 healthy volunteers aged 18–55 years, as previously described.[5] Briefly, healthy adult participants were enrolled after screening to exclude those with pre-existing health conditions. Participants were randomly assigned 1:1 to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles (standard dose), measured using spectrophotometry, or meningococcal group A, C, W, and Y conjugate vaccine (MenACWY) as control. An open-label non-randomised subgroup of ten participants were given two doses of ChAdOx1 nCoV-19 28 days apart, as previously reported.[5] This study was originally planned as a single-dose study and 88 participants in the phase 1 part of the study remain recipients of a single dose. However, the protocol was modified to a two-dose regime, following an amendment on July 30, 2020 (version 9.0; appendix 2 pp 180–181), for the remaining phase 2 cohorts as a result of robust booster responses identified in the evaluation of the early immunogenicity cohorts, with the booster dose given at the earliest possible time.[5]

COV002 (UK)

COV002 is a continuing single-blind phase 2/3 study in the UK that began on May 28, 2020, and enrolled participants in 19 study sites in England, Wales, and Scotland. Enrolment particularly targeted individuals working in professions with high possible exposure to SARS-CoV-2, such as health and social care settings.

Two dosage groups were included in COV002: participants who received a low dose of the vaccine ($2\cdot2\times10^{10}$ viral particles) as their first dose and were boosted with a standard dose (in the LD/SD group), and subsequent cohorts who were vaccinated with two standard-dose vaccines (SD/SD group). Initial dosing in COV002 was with a batch manufactured at a contract manufacturing organisation using chromatographic purification. During quality control of this second batch, differences were observed between the quantification methods (spectrophotometry and quantitative PCR [qPCR]) prioritised by different manufacturing sites. In consultation with the national regulator (Medicines and Healthcare products Regulatory Agency), we selected a dose of 5×10^{10} viral particles by spectrophotometer ($2\cdot2\times10^{10}$ viral particles by qPCR), in order to be consistent with the use of spectrophotometry in the phase 1 study (COV001),[5] and to ensure the dose was within a safe and immunogenic range according to measurements by both methods. A lower-than-anticipated reactogenicity profile was noted in the trial, and unexpected interference of an excipient with the spectrophotometry assay was identified. After review and approval by the regulator, it was concluded that the qPCR (low-dose) reading was more accurate and further doses were adjusted to the standard dose (5×10^{10} viral particles) using a qPCR assay. The protocol was amended on June 5, 2020, resulting in enrolment of two distinct groups with different dosing regimens with no pause in enrolment (version 6.0; appendix 2 p 330). A suite of assays has now been developed for characterisation of concentration (which confirmed the low and standard dosing), and future batches are all released with a specification dose of $3\cdot5–6\cdot5\times10^{10}$ viral particles, and this was used for the booster doses in the efficacy analysis presented here.

The LD/SD cohort (aged 18–55 years) was enrolled over 11 days between May 31 and June 10, 2020. The SD/SD cohort (aged 18–55 years) was enrolled from June 9 to July 20, 2020. Subsequently, enrolment of older age cohorts began (from Aug 8, 2020, for participants aged 56–69 years and from Aug 13, 2020, for participants aged ≥70 years), all of whom were assigned to two standard doses (SD/SD cohort). Each site implemented the protocol amendment before changing from low-dose administration to standard-dose administration, and therefore there was no overlap in enrolment of participants in these cohorts.

The 18–55-year-old cohorts were originally planned as single-dose efficacy cohorts. However, the protocol was modified on July 20, 2020, to offer a second dose to the participants in these cohorts as a result of robust booster responses identified in the evaluation of the early immunogenicity cohorts (version 9.0; appendix 2 pp 331–332).[5] Boosting began on Aug 3, 2020, resulting

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See **Online** for appendix 1

See **Online** for appendix 2

in a longer gap between prime and booster vaccines in these cohorts than for those aged 55–69 years and those aged 70 years or older, as these participants were enrolled into two-dose groups from the start.

Results for participants enrolled into immunogenicity subgroups have been previously published, including a small subset who received a low-dose boost.[6] Full details are available in the study protocol (appendix 2 pp 184–342) and the procedures have been previously described.[6]

COV003 (Brazil)

COV003 is a continuing single-blind phase 3 study in Brazil that began on June 23, 2020. The focus of recruitment was targeted at those at high risk of exposure to the virus, including health-care workers at six sites across Brazil. Participants were aged 18 years or older, and this trial included individuals with stable pre-existing health conditions. All participants were offered two doses of the vaccine at a dose of $3 \cdot 5–6 \cdot 5 \times 10^{10}$ viral particles with administration up to 12 weeks apart (target 4 weeks), following a protocol amendment on July 28, 2020, to include booster groups (version 4.0; appendix 2 pp 438–439). Full details are available in the study protocol (appendix 2 pp 343–441).

COV005 (South Africa)

COV005 is a continuing double-blind phase 1/2 study in South Africa in healthy adults aged 18–65 years living without HIV that began on June 28, 2020. An additional immunogenicity cohort of those living with HIV was also enrolled but are not included in this interim analysis. All participants were offered two doses of the vaccine at a dose of $3 \cdot 5–6 \cdot 5 \times 10^{10}$ viral particles, with doses administered 4 weeks apart. A small subgroup of 44 participants received a half-dose vaccine (21 as their first dose and 23 as their second dose) as a result of variability in the release assay, before the adoption of new methods for characterisation of concentration. Adjustment in dose was discussed with and approved by the national regulator. Full details are available in the study protocol (appendix 2 pp 442–559).

A combined independent data safety monitoring board reviews safety data from all four trials on a regular basis.

Randomisation and masking

In efficacy cohorts for all studies, participants were randomised 1:1 to receive ChAdOx1 nCoV-19 or a control product. In COV002, MenACWY was chosen as the control group vaccine to minimise the chance of accidental participant unmasking due to local or systemic reactions to the vaccine. COV003 used MenACWY as the control for the first dose and saline for the second dose. In COV005, participants randomly assigned to the control group were administered saline solution. Randomisation lists were prepared by the study statistician (MV) using block randomisation, stratified by study site and study group, and uploaded into to the secure web platform used for the study electronic case report form (REDCap version 9.5.22) for COV001, COV002, and COV003. In COV005, the randomisation list was held by the unmasked study pharmacist who prepared the vaccines for administration, with all other trial staff masked to group allocation. The trial staff administering the vaccine prepared vaccines out of sight of the participants and syringes were covered with an opaque material until ready for administration to ensure masking of participants.

Procedures

The recombinant adenovirus for ChAdOx1 nCoV-19 was manufactured and vialed by Advent (Pomezia, Italy), and additional batches produced by COBRA Biologics (Keele, UK) and vialed by Symbiosis (Sterling, UK). Both were manufactured according to Good Manufacturing Practice and approved by the regulatory agency in the UK, the Medicines and Healthcare products Regulatory Agency.

Baseline assessments included review of inclusion and exclusion criteria, medical history, vital signs measurement, history-directed clinical examination, and collection of serum for SARS-CoV-2 serology.

Participants across all four trials were asked to contact the study site if they experienced specific symptoms associated with COVID-19 and received regular reminders to do so. Those who met symptomatic criteria had a clinical assessment, a swab taken for a nucleic acid amplification test (NAAT), and blood samples taken for safety and immunogenicity. In the UK and Brazil, the list of qualifying symptoms for swabbing included any one of the following: fever of at least 37·8°C, cough, shortness of breath, and anosmia or ageusia. In South Africa, the list of qualifying symptoms for swabbing was broader, and additionally included myalgia, chills, sore throat, headache, nasal congestion, diarrhoea, runny nose, fatigue, nausea, vomiting, and loss of appetite.

In all studies, if participants were tested outside of the trial, either in their workplace if a health-care worker or by private providers, these results were recorded and assessed by a masked independent endpoint review committee. The source of each swab was recorded plus the details of the test kit where available.

To test for asymptomatic infections, participants in COV002 in the UK were asked to provide a weekly self-administered nose and throat swab for NAAT testing from 1 week after first vaccination using kits provided by the UK Department of Health and Social Care (DHSC). Participants were given home test kits provided by the DHSC that included step-by-step instructions on how to do a self-swab and a link to a demonstration video. The site trial team provided support with logistics of packaging and returning test kits and tracking swab results to participants if required. Swabs were taken by participants in their homes and posted to dedicated DHSC testing laboratories for processing. Participants were directly informed of their results by text or email from the National Health Service (NHS). Swab results

from participants in England and Wales were provided to the trial statistician on a daily basis by the NHS and matched to individuals based on personal identification data (name, date of birth, NHS number, and postcode). Swab results from participants in Scotland were unavailable to the study team at the time of the data cutoff for this analysis, but will be included in future analyses. Any swab results that were not able to be matched to a study participant using at least two pieces of personal data were not added to the study database.

In Brazil, there was no testing plan for asymptomatic infections. In South Africa, asymptomatic infections were detected from swabs obtained at study visits attended, but are not summarised here as there were only a small number of timepoints for detection of these cases.

All cases of COVID-19 were reviewed by two members of a masked independent clinical review team who assessed clinical details, including medical history, symptoms, adverse events, and swab results, and assigned severity scores according to the WHO clinical progression scale.[8]

For symptomatic participants in COV002 in the UK, weekly swabbing continued both before and after participants reported symptoms to the study site. Thus, a participant who reported symptoms and was clinically assessed might also have had additional swabs return positive results through the asymptomatic testing process for several weeks. In addition, due to the large number of health-care workers enrolled in these studies, some participants were tested according to their workplace testing policies and these results were also entered into the database for review by the masked endpoint evaluation committee. Further exploratory assessment of the length of time participants remained NAAT-positive, and the sources of information used for case detection will be done in future analyses.

Outcomes

The primary objective was to evaluate the efficacy of ChAdOx1 nCoV-19 vaccine against NAAT-confirmed COVID-19. The primary outcome was virologically confirmed, symptomatic COVID-19, defined as a NAAT-positive swab combined with at least one qualifying symptom (fever ≥37·8°C, cough, shortness of breath, or anosmia or ageusia).

All participants were given an emergency 24-h telephone number to contact the on-call study physician for the duration of the study to report any illnesses. Serious adverse events were recorded throughout the study and reviewed at each study visit, with causality assigned by the site investigator. Events were clinically coded according to the Medical Dictionary for Regulatory Activities.

Statistical analysis

The plan for assessing efficacy and safety for the ChAdOx1 nCoV-19 vaccine is based on global analyses using all available data from four studies with analysis pooled across the studies. A global statistical analysis plan for pooling study data was developed, after extensive advice from regulators, to prespecify the analyses that would contribute to the assessment of efficacy and this was signed off before any data analysis was conducted.

Randomised participants who received at least one dose in all studies are included in the safety analysis. However, each study had to meet prespecified criteria of having at least five cases eligible for inclusion in the primary outcome before a study was included in efficacy analyses. Neither COV001 or COV005 met these criteria and so are not included in the efficacy assessment for this interim analysis. It is expected that they will be included in efficacy assessments in future analyses once more cases have accrued. Additionally, only efficacy groups for COV002 (ie, groups 4, 6, 9, and 10) were included.

Vaccine efficacy was calculated as 1– adjusted relative risk (ChAdOx1 nCoV-19 *vs* control groups) computed using a Poisson regression model with robust variance.[9] The model contained terms for study, treatment group, and age group (18–55, 56–69, and ≥70 years) at randomisation. A reduced model that did not contain a term for age was used for models affected by convergence issues due to having few cases in the older age groups. The logarithm of the period at risk for the primary endpoint for pooled analysis was used as an offset variable in the model to adjust for volunteers having different follow-up times during which the events occurred. Cumulative incidence is presented using the Kaplan-Meier method.

The global pooled analysis plan allowed for an interim and a final efficacy analysis with α adjusted between the two analyses using a flexible gamma α-spending function, with significance being declared if the lower bound of the (1–α)% CI is greater than 20%. Evidence of efficacy at the time of the interim analysis was not considered reason to stop the trials and all trials are continuing to accrue further data that will be included in future analyses.

The first interim analysis was planned to be triggered when at least 53 cases in participants who had received two standard-dose vaccines (SD/SD) had accrued that met the primary outcome definition more than 14 days after the second dose. This analysis provides 77% power for the 20% threshold to assume a true vaccine efficacy of 70%. Although the number of cases in the SD/SD cohort was used as the trigger for the interim analysis, the prespecified primary analysis included both SD/SD and LD/SD recipients. Due to the rapid increase in incidence of COVID-19 in the UK in October, more than 53 cases had accrued by the time of data lock for this interim analysis. There were 98 cases available for inclusion in the SD/SD cohorts. Based on these numbers, the α level calculated using the gamma α-spending function for this analysis is 4·16%.

Participants were excluded from the primary efficacy analysis if they were seropositive at baseline or had no baseline result. Other exclusions included those with NAAT-positive swabs within 14 days after the second vaccination, or those who discontinued from the study before having met the primary efficacy endpoint with a follow-up time of less than 15 days after the second vaccination. All reasons for exclusion are shown in appendix 1 (pp 5–8).

An analysis of efficacy after the first standard-dose vaccine in those who only received standard-dose vaccines was undertaken as a secondary analysis. Individuals were excluded if they had a NAAT-positive swab within 21 days after their first standard-dose vaccine.

Participants were analysed according to the vaccines they received. Sensitivity analyses included those who were seropositive at baseline and an intention-to-treat analysis. Safety analyses include all randomised participants who received at least one dose of any vaccine in any study.

Prespecified subgroup analyses are not included in this report but will be presented in future analyses when a larger dataset is available. However, in response to reviewer and editorial comments, a small number of exploratory subgroup comparisons has been included to explore differences in efficacy in the LD/SD and SD/SD groups and potential confounder variables. The LD/SD cohort in the UK comprised participants aged 18–55 years who received their second dose after a substantial gap. Age and the time difference between vaccines were therefore potential confounders and were explored further in subgroup analyses, restricted to those aged 18–55 years, those with more than 8 weeks' interval between vaccine doses, and a comparison of those in the SD/SD cohort receiving vaccines at short (<6 weeks) or long (≥6 weeks) intervals. Subgroup comparisons were done by incorporating the treatment-by-subgroup interaction term in the model and reporting the p value for the interaction term.

Data analysis was done using R (version 3.6.1 or later). Robust Poisson models were fitted using the PROC GENMOD function in SAS (version 9.4). The α level for the analysis was calculated using the gsDesign function in R. The cutoff date for inclusion in the analysis was Nov 4, 2020, and the data lock date was Nov 21, 2020.

The four trials are registered at ISRCTN89951424 (COV003) and ClinicalTrials.gov, NCT04324606 (COV001), NCT04400838 (COV002), and NCT04444674 (COV005).

Role of the funding source

AstraZeneca reviewed the data from the study and the final manuscript before submission, but the academic authors

	COV002 (UK; LD/SD; N=2741)		COV002 (UK; SD/SD; N=4807)		COV003 (Brazil; all SD/SD; N=4088)	
	ChAdOx1 nCoV-19 (n=1367)	MenACWY (n=1374)	ChAdOx1 nCoV-19 (n=2377)	MenACWY (n=2430)	ChAdOx1 nCoV-19 (n=2063)	MenACWY plus saline (n=2025)
Age, years						
18–55	1367 (100·0%)	1374 (100·0%)	1879 (79·0%)	1922 (79·1%)	1843 (89·3%)	1833 (90·5%)
56–69	0	0	285 (12·0%)	293 (12·1%)	209 (10·1%)	187 (9·2%)
≥70	0	0	213 (9·0%)	215 (8·8%)	11 (0·5%)	5 (0·2%)
Sex						
Female	886 (64·8%)	927 (67·5%)	1378 (58·0%)	1437 (59·1%)	1261 (61·1%)	1156 (57·1%)
Male	481 (35·2%)	447 (32·5%)	999 (42·0%)	993 (40·9%)	802 (38·9%)	869 (42·9%)
BMI, kg/m²	25·2 (22·8–28·7)	25·3 (22·7–28·8)	25·4 (22·9–28·7)	25·5 (22·9–29·1)	25·6 (22·8–29·1)	25·6 (23·1–29·0)
Ethnicity						
White	1257 (92·0%)	1278 (93·0%)	2153 (90·6%)	2214 (91·1%)	1357 (65·8%)	1366 (67·5%)
Black	6 (0·4%)	2 (0·1%)	17 (0·7%)	14 (0·6%)	230 (11·1%)	210 (10·4%)
Asian	76 (5·6%)	59 (4·3%)	137 (5·8%)	138 (5·7%)	54 (2·6%)	53 (2·6%)
Mixed	19 (1·4%)	22 (1·6%)	48 (2·0%)	42 (1·7%)	410 (19·9%)	386 (19·1%)
Other	9 (0·7%)	13 (0·9%)	22 (0·9%)	22 (0·9%)	12 (0·6%)	10 (0·5%)
Health and social care setting workers	1236 (90·4%)	1253 (91·2%)	1441 (60·6%)	1513 (62·3%)	1833 (88·9%)	1775 (87·7%)
Comorbidities						
Cardiovascular disease	104 (7·6%)	92 (6·7%)	264 (11·1%)	266 (10·9%)	271 (13·1%)	244 (12·0%)
Respiratory disease	158 (11·6%)	176 (12·8%)	285 (12·0%)	316 (13·0%)	215 (10·4%)	210 (10·4%)
Diabetes	18 (1·3%)	15 (1·1%)	58 (2·4%)	60 (2·5%)	59 (2·9%)	60 (3·0%)

Data are n (%) or median (IQR). The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in the corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed severe acute respiratory syndrome coronavirus 2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. BMI=body-mass index.

Table 1: **Baseline characteristics of participants included in the primary efficacy population, by study and dosing strategy**

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

Vaccine efficacy was calculated from the robust Poisson model. The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in a corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. NAAT=nucleic acid amplification test. *CIs are 95% unless indicated otherwise. †95·8% CI used for primary analysis. ‡Vaccine efficacy calculated from a reduced robust Poisson model that was not adjusted for age. All other models included an adjustment for age. §p value for interaction term comparing LD/SD with SD/SD is p=0·010. ¶Other non-primary symptomatic COVID-19 disease includes cases who have symptoms other than the five main symptoms that are required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia).

Table 2: **Efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

retained editorial control. All other funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 23 and Nov 4, 2020, 23 848 participants were recruited and vaccinated across the four studies: 1077 in COV001 (UK), 10 673 in COV002 (UK), 10 002 in COV003 (Brazil), and 2096 in COV005 (South Africa). 11 636 participants in COV002 and COV003 met the inclusion criteria for the primary analysis, 5807 of whom received two doses of ChAdOx1 nCoV-19 and 5829 of whom received two doses of control product. A trial profile and reasons for exclusion from the primary analysis are shown in appendix 1 (pp 5–7). Here, we provide safety data on 74 341 person-months of follow-up after first dose (median 3·4 months, IQR 1·3–4·8) and 29 060 person-months of follow-up after two doses (median 2·0, 1·3–2·3).

Of the participants in COV002 and COV003 included in the primary efficacy analyses, the majority were aged 18–55 years (6542 [86·7%] of 7548 in the UK and 3676 [89·9%] of 4088 in Brazil; table 1). Those aged 56 years or older were recruited later and contributed 12·2% of the total cohort in the current analysis (1006 [13·3%] in the UK and 412 [10·1%] in Brazil). 7045 (60·5%) participants were female. 6902 (91·4%) participants in the UK and 2723 (66·6%) participants in Brazil were white (table 1). Baseline participants of the safety population are shown in appendix 1 (pp 9–10).

The timing of priming and booster vaccine administration varied between studies. As protocol amendments to add a booster dose took place when the trials were underway, and owing to the time taken to manufacture and release a new batch of vaccine, doses could not be administered at a 4-week interval. 1459 (53·2%) of 2741 participants in COV002 in the LD/SD group received a second dose at least 12 weeks after the first (median 84 days, IQR 77—91) and only 22 (0·8%) received a second dose within 8 weeks of the first. The median interval between doses for the SD/SD group in COV002 was 69 days (50–86). Conversely, the majority of participants in COV003 in the SD/SD group (2493 [61·0%] of 4088) received a second dose within 6 weeks of the first (median 36 days, 32–58; appendix 1 p 11).

A small proportion of participants were seropositive at baseline (138 [1·3%] of 10 673 in the UK and 235 [2·3%] of 10 002 in Brazil). Three participants seropositive at baseline had subsequent NAAT-positive swabs. One participant had an asymptomatic infection 3 weeks after a first dose of ChAdOx1 nCoV-19. Two other participants in the control group had symptomatic infections 8 weeks and 21 weeks after their baseline sample was taken.

There were 131 cases of symptomatic COVID-19 in LD/SD or SD/SD recipients who were eligible for inclusion in the primary efficacy analysis more than 14 days after the second dose of vaccine (table 2). There were 30 (0·5%) cases among 5807 participants in the vaccine arm and 101 (1·7%) cases among 5829 participants in the control group, resulting in vaccine efficacy of 70·4% (95·8% CI 54·8–80·6; table 2; figure). In participants who received two standard-dose vaccines, vaccine efficacy was 62·1% (95% CI 41·0–75·7), whereas in those who received a low dose as their first dose of vaccine, efficacy was higher at 90·0% (67·4–97·0; $p_{interaction}$=0·010; table 2; appendix 1 pp 12–13).

In England and Wales, 129 529 weekly self-swabs were processed by the DHSC, of which 126 324 (97·5%) were matched to study participants. There were 435 positive swabs, of which 354 (81·4%) were matched. Symptoms in these participants were not routinely assessed as swabs were done at home and sent for testing through the post. Asymptomatic infections or those with unreported symptoms were detected in 69 participants (table 2). Vaccine efficacy in the 24 LD/SD recipients was 58·9% (95% CI 1·0 to 82·9), whereas it was 3·8% (–72·4 to 46·3) in the 45 participants receiving SD/SD (table 2).

Results from sensitivity analyses, including participants who were seropositive at baseline and by intention to treat, were very similar to main results (data not shown).

Results from the subgroup comparisons presented in this analysis were similar to overall results (table 3). In the SD/SD UK cohort who were aged 18–55 years, 49 cases were available for inclusion in the analysis and vaccine efficacy was 59·3% (95% CI 25·1 to 77·9; $p_{interaction}$=0·019; table 3). When further restricted to those who received their vaccines more than 8 weeks apart, 33 cases were included in the SD/SD analysis and vaccine efficacy was 65·6% (24·5 to 84·4; $p_{interaction}$=0·082; table 3; appendix 1 pp 12–13). In the SD/SD cohorts in the UK and Brazil, vaccine efficacy was similar when analysed in subgroups according to time between

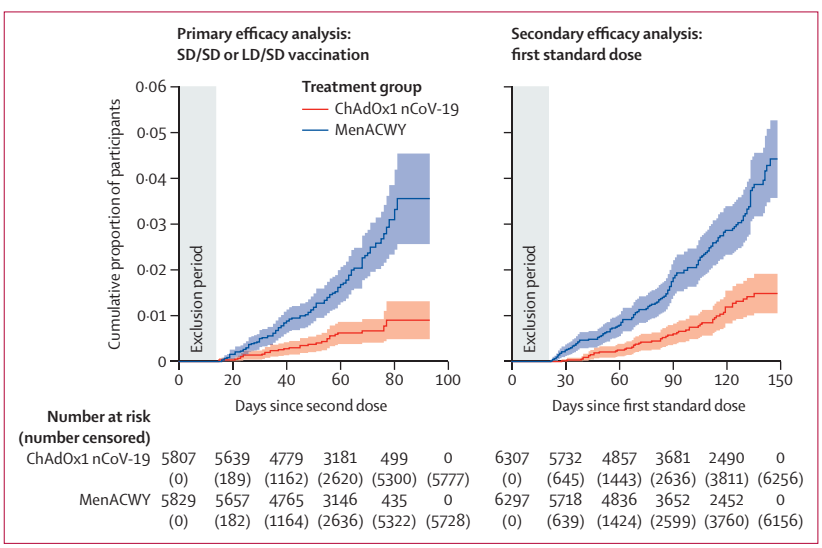

Figure: **Kaplan-Meier cumulative incidence of primary symptomatic, NAAT-positive COVID-19**
Cumulative incidence of symptomatic COVID-19 after two doses (left) or after first standard dose in participants receiving only standard-dose vaccines (right). Grey shaded areas show the exclusion period after each dose in which cases were excluded from the analysis. Blue and red shaded areas show 95% CIs. LD/SD=low-dose prime plus standard-dose boost. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid amplification test. SD/SD=two standard-dose vaccines given.

	Total number of cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)	p value for interaction
COV002 (UK), age 18–55 years*	..	..	..	..	0·019
LD/SD recipients	33	3/1367 (0·2%)	30/1374 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	49	14/1879 (0·7%)	35/1922 (1·8%)	59·3% (25·1 to 77·9)	..
COV002 (UK), age 18–55 years with >8 weeks' interval between vaccine doses*	..	..	..	..	0·082
LD/SD recipients	33	3/1357 (0·2%)	30/1362 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	34	8/1407 (0·6%)	26/1512 (1·7%)	65·6% (24·5 to 84·4)	..
All SD/SD (UK and Brazil)†	..	..	..	..	0·557
<6 weeks' interval between vaccine doses	28	9/1702 (0·5%)	19/1698 (1·1%)	53·4% (–2·5 to 78·8)	..
≥6 weeks' interval between vaccine doses	70	18/2738 (0·7%)	52/2757 (1·9%)	65·4% (41·1 to 79·6)	..

Cohorts are all subsets of the primary efficacy population. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. BMI=body-mass index. *Models adjusted for BMI (<30 *vs* ≥30 kg/m^2), health-care worker status (yes *vs* no), and ethnicity (white *vs* non-white). †Model adjusted for BMI (<30 *vs* ≥30 kg/m^2), health-care worker status (yes *vs* no), ethnicity (white *vs* non-white), age (<56 years *vs* ≥56 years), and study (COV002 *vs* COV003).

Table 3: **Subgroup comparisons of efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (95% CI)
		n/N (%)	Incidence per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence per 1000 person-years (person-days of follow-up)	
COV002 (UK)	90	28/3060 (0·9%)	35·4 (288 955)	62/3064 (2·0%)	78·5 (288 395)	55·0% (29·7 to 71·1)
COV003 (Brazil)	102	23/3247 (0·7%)	46·7 (179 743)	79/3233 (2·4%)	162·4 (177 693)	71·2% (54·2 to 81·9)
Primary symptomatic COVID-19*	192	51/6307 (0·8%)	39·7 (468 698)	141/6297 (2·2%)	110·5 (466 088)	64·1% (50·5 to 73·9)
Other non-primary symptomatic COVID-19†	21	12/6307 (0·2%)	9·4 (468 698)	9/6297 (0·1%)	7·1 (466 088)	−32·8% (−214·8 to 44·0)‡
Any symptomatic COVID-19	213	63/6307 (1·0%)	49·1 (468 698)	150/6297 (2·4%)	117·5 (466 088)	58·3% (44·0 to 68·9)
Asymptomatic or symptoms unknown (COV002)	71	34/2751 (1·2%)	46·8 (265 142)	37/2760 (1·3%)	51·0 (264 994)	7·8% (−46·7 to 42·1)
Any NAAT-positive swab	291	102/6307 (1·6%)	79·5 (468 698)	189/6297 (3·0%)	148·1 (466 088)	46·3% (31·8 to 57·8)

Vaccine efficacy was calculated from the robust Poisson model. The first-standard-dose efficacy population includes participants seronegative at baseline who received only standard dose vaccines or were in the corresponding control group, and remained on study 22 days after their first dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. NAAT=nucleic acid amplification test. *NAAT-positive swab plus at least one of cough, shortness of breath, fever higher than 37·8°C, anosmia, or ageusia. †Other non-primary symptomatic COVID-19 disease includes cases that have symptoms other than the five main symptoms required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia). ‡Vaccine efficacy was calculated from a reduced robust Poisson model (excluding the age group category due to the full model failing to converge). Participants with a low-dose prime were excluded.

Table 4: **Efficacy against SARS-CoV-2 more than 21 days after the first standard dose in seronegative participants who received only standard doses**

vaccines, at 53·4% (−2·5 to 78·8) in participants with less than 6 weeks' interval between doses and 65·4% (41·1 to 79·6) in participants with at least 6 weeks' interval ($p_{interaction}$=0·56; table 3).

For our secondary analysis of cases occurring more than 21 days after the first standard dose in participants who received only standard doses, there were 192 included cases with a vaccine efficacy of 64·1% (95% CI 50·5–73·9; table 4; figure)

More than 21 days after their first dose, ten participants were hospitalised due to COVID-19 (defined as WHO clinical progression score ≥4), two of whom were assessed as having severe COVID-19 (WHO score ≥6), including one fatal case. All ten cases were in the control group (table 5).

Five cases included in the primary analysis occurred in those participants older than 55 years of age. Vaccine efficacy in older age groups could not be assessed but will be determined, if sufficient data are available, in a future analysis after more cases have accrued.

Across all four studies, the vaccine had a good safety profile with serious adverse events and adverse events of special interest balanced across the study arms. Serious adverse events occurred in 168 participants, 79 of whom received ChAdOx1 nCoV-19 and 89 of whom received MenACWY or saline control (appendix 1 pp 15–18). There were 175 events (84 in the ChAdOx1 nCoV-19 group and 91 in the control group), three of which were considered possibly related to either the experimental or a control vaccine. A case of haemolytic anaemia in the control group in the UK phase 1/2 study occurring 10 days after MenACWY vaccine was considered possibly related to the intervention and has been previously described.[5] A case of transverse myelitis was reported

	ChAdOx1 nCoV-19 (n=12 021)	MenACWY or saline control (n=11 724)
Hospitalisation (WHO clinical progression score ≥4)		
≤21 days after the first dose	2*	6
>21 days after the first dose and ≤14 days after the second dose	0	5
>14 days after the second dose	0	5
Severe COVID-19 (WHO clinical progression score ≥6)		
≤21 days after the first dose	0	0
>21 days after the first dose and ≤14 days after the second dose	0	1
>14 days after the second dose	0	1

The safety population includes all randomisation participants who received at least one dose of vaccine. Severe COVID-19 (WHO score ≥6) is a subset of hospitalisations (WHO score ≥4). Cases were eligible for inclusion in efficacy if the first symptom or first NAAT-positive result was on or before the data cutoff date (Nov 4, 2020). Two cases appear in this table that do not appear in the table for serious adverse events in appendix 1 (pp 15–20) as the adverse event reporting date was after the data cutoff date. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid amplification test. *One case on the day of the first vaccination and one case 10 days after the first dose.

Table 5: **Hospitalisation for COVID-19 and severe COVID-19 in the safety population**

14 days after ChAdOx1 nCoV-19 booster vaccination as being possibly related to vaccination, with the independent neurological committee considering the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination. A potentially vaccine-related serious adverse event was reported 2 days after vaccination in South Africa in an individual who recorded fever higher than 40°C, but who recovered

rapidly without an alternative diagnosis and was not admitted to hospital. The participant remains masked to group allocation, continues in the trial, and received a second dose of the allocated vaccine without a similar reaction.

There were two additional cases of transverse myelitis that were originally reported as potentially related but later determined to be unlikely to be related to vaccination by an independent committee of neurological experts. One case that occurred 10 days after a first vaccination with ChAdOx1 nCoV-19 was initially assessed as possibly related, but later considered unlikely to be related by the site investigator when further investigation revealed pre-existing, but previously unrecognised, multiple sclerosis. The second case was reported 68 days after MenACWY vaccination. While considered possibly related by the site investigator at the time of reporting, an independent panel of neurological experts considered this to be unlikely. All trial participants have recovered, or are in a stable or improving condition.

There were four non-COVID-19 deaths reported across the studies (three in the control arm and one in the ChAdOx1 nCoV-19 arm) that were all considered unrelated to the vaccine, with cause of death assessed as road traffic accident, blunt force trauma, homicide, and fungal pneumonia.

Discussion

Here, we present the first interim safety and efficacy data for a viral vector coronavirus vaccine, ChAdOx1 nCoV-19, evaluated in four trials across three continents, showing significant vaccine efficacy of 70·4% after two doses and protection of 64·1% after at least one standard dose, against symptomatic disease, with no safety concerns.

The prespecified analysis population, which was determined following feedback from national and international regulators before unblinding of the study, included a pooled analysis from several countries to improve generalisability, and inclusion of two dose subgroups within the UK trial. This pooling strategy was authorised by the chief investigator (AJP) and study statistician (MV), with no concerns about pooling different control groups, and was accepted by regulators involved in the discussions. There had been initial concern that the LD/SD regimen might have lower efficacy than SD/SD, and the regulatory authority acceptance of the inclusion of the two trial regimens (LD/SD and SD/SD) in analysis was based on the observation that these regimens generated similar levels of binding antibody, and would therefore increase the sample size available for analysis without compromising efficacy. The discussion about pooling and inclusion of LD/SD was made at a time when disease rates were low in the UK and, in the face of the pandemic, it was agreed that pooling could provide the earliest possible read on efficacy that could contribute to public health.

No previous trials have been published on the efficacy of a viral-vectored coronavirus vaccine and so this study provides the first peer-reviewed evidence that induction of immune responses against spike protein using viral vectors provides protection against the disease in humans, as has been seen in animal models.

In participants who received two standard doses, efficacy against primary symptomatic COVID-19 was consistent in both the UK (60·3% efficacy) and Brazil (64·2% efficacy), indicating these results are generalisable across two diverse settings with different timings for the booster dose (with most participants in the UK receiving the booster dose more than 12 weeks after the first dose and most participants in Brazil receiving their second dose within 6 weeks of the first). Exploratory subgroup analyses included at the request of reviewers and editors also showed no significant difference in efficacy estimates when comparing those with a short time window between doses (<6 weeks) and those with longer (≥6 weeks), although further detailed exploration of the timing of doses might be warranted.

Efficacy of 90·0% seen in those who received a low dose as prime in the UK was intriguingly high compared with the other findings in the study. Although there is a possibility that chance might play a part in such divergent results, a similar contrast in efficacy between the LD/SD and SD/SD recipients with asymptomatic infections provides support for the observation (58·9% [95% CI 1·0 to 82·9] *vs* 3·8% [–72·4 to 46·3]). Exploratory subgroup analyses, included at the request of reviewers and editors, that were restricted to participants aged 18–55 years, or aligned (>8 weeks) intervals between doses, showed similar findings. Use of a low dose for priming could provide substantially more vaccine for distribution at a time of constrained supply, and these data imply that this would not compromise protection. While a vaccine that could prevent COVID-19 would have a substantial public health benefit, prevention of asymptomatic infection could reduce viral transmission and protect those with underlying health conditions who do not respond to vaccination, those who cannot be vaccinated for health reasons, and those who will not or cannot access a vaccine, providing wider benefit for society. However, the wide CIs around our estimates show that further data are needed to confirm these preliminary findings, which will be done in future analyses of the data accruing in these ongoing trials.

Similar results have been seen for other vaccines where a reduced number or type of priming dose in infancy can lead to higher responses to a booster vaccine.[10] Further work is needed to determine the mechanism of the increased efficacy with a LD/SD regimen, which might be due to higher levels of neutralising antibody, lower levels of anti-vector immunity with lower vector-derived antigen content of the first dose, or differential antibody functionality or cellular immunity, including altered avidity or immunodominance.

Other coronavirus vaccine developers have released preliminary high-level results in public statements, including more than 90% efficacy reported for the lipid nanoparticle mRNA vaccine BNT162b2,[11] 92% efficacy for the Sputnik V vaccine (developed at the National Research Centre for Epidemiology and Microbiology),[12] and 94·5% for the Moderna lipid nanoparticle mRNA-1273 vaccine.[13] The possibility that more than one efficacious vaccine against COVID-19 might be approved for use in the near future is encouraging. However, control of pandemic coronavirus will only be achieved if the licensure, manufacturing, and distribution of these vaccines can be achieved at an unprecedented scale and vaccination is rolled out to all those who are vulnerable.

The US Food and Drug Administration's guidelines indicate that they would license a vaccine against the pandemic virus that showed at least 50% efficacy[14] and WHO have indicated a minimum efficacy of 50% in its target product profile.[15] A modelling study found that a vaccine with efficacy of 60–80% could allow reduction in physical distancing measures, but this would still require high coverage.[16] The findings here indicate that the efficacy of ChAdOx1 nCoV-19 exceeds these thresholds and has the potential to have a public health impact.

Much consideration has been given to the statistical confidence in vaccine efficacy estimates, given the size of the global population who might be vaccinated. To ensure that point estimates of efficacy in clinical trials are sufficiently robust, some regulatory authorities consider that the lower bound of the CI for efficacy should be higher than 20% (personal communication), with other authorities more stringent and anticipating a lower bound of 30% for licensure.[14] Here, we present data that exceed both these thresholds in the pooled analysis, which we had agreed with regulators before unblinding of the study, and also meet the thresholds set in the individual analyses of trials by country and by study arm.

We designed our studies early in the pandemic and fixed our primary symptomatic disease endpoint on the basis of expert analysis and guidelines from Public Health England and WHO as the first wave of disease spread around the world, although these have now been substantially updated.[17,18] We have used a restricted definition of symptomatic disease, since many other symptoms that are associated with COVID-19 disease are non-specific. Since endpoints in protocols for different vaccines are not well aligned, we recognise that it will be difficult to compare efficacy across programmes. However, we have also included hospital admissions and severe disease as an endpoint in the current study, which might be easier to assess in comparison with other vaccines, and found that in the ten cases available for analysis more than 21 days after the first dose, there was complete protection against hospitalisation for COVID-19.

While the data presented here show that ChAdOx1 nCov-19 is efficacious against symptomatic disease, with most cases accruing in adults younger than 55 years of age so far, an important public health consideration is the morbidity and mortality of the disease in an older adult population and thus the potential efficacy in this age group. We have reported immunogenicity data showing similar immune responses following vaccination with two doses of ChAdOx1 nCov-19 in older adults, including those older than 70 years of age, when compared with those younger than 55 years.[6] As older age groups were recruited later than younger age groups, there has been less time for cases to accrue and as a result, efficacy data in these cohorts are currently limited by the small number of cases, but additional data will be available in future analyses.

These trials, conducted on three different continents, enrolled geographically and ethnically diverse populations. Severe COVID-19 has been seen to disproportionately affect people of non-white ethnicity, as well as those who are male, overweight, and the elderly.[19,20]

In our studies, the demographic characteristics of those enrolled varied between countries. In the UK, the enrolled population was predominantly white and, in younger age groups, included more female participants due to the focus on enrolment of health-care workers. This is a typically lower risk population for severe COVID-19. The demographic profile combined with the weekly self-swabbing for asymptomatic infection in the UK results in a milder case-severity profile. In Brazil, there was a larger proportion of non-white ethnicities, and again the majority of those enrolled were health-care workers.

We have previously reported on the local and systemic reactogenicity of ChAdOx1 nCoV-19 and shown that it is tolerated and that the side-effects are less both in intensity and number in older adults, with lower doses, and after the second dose. Although there were many serious adverse events reported in the study in view of the size and health status of the population included, there was no pattern of these events that provided a safety signal in the study. Three cases of transverse myelitis were initially reported as suspected unexpected serious adverse reactions, with two in the ChAdOx1 nCoV-19 vaccine study arm, triggering a study pause for careful review in each case. Independent clinical review of these cases has indicated that one in the experimental group and one in the control group are unlikely to be related to study interventions, but a relationship remained possible in the third case. Careful monitoring of safety, including neurological events, continues in the trials. All safety data will be provided to regulators for review.

In this interim analysis, we have not been able to assess duration of protection, since the first trials were initiated in April, 2020, such that all disease episodes have accrued within 6 months of the first dose being administered. Further evidence will be required to determine duration of protection and the need for additional booster doses of vaccine.

The results presented in this Article constitute the key findings from the first interim analysis, which are

provided for rapid review by the public and policy makers. In future analyses with additional data included as they accrue, we will investigate differences in key subgroups such as older cohorts, ethnicity, dose regimen, and timing of booster vaccines, and we will search for correlates of protection.

Until widespread immunity halts the spread of SARS-CoV-2, physical distancing measures and novel therapies are needed to control COVID-19. In the meantime, an efficacious vaccine has the potential to have a major impact on the pandemic if used in populations at risk of severe disease. Here, we have shown for the first time that a viral vector vaccine, ChAdOx1 nCoV-19, is efficacious and could contribute to control of the disease in this pandemic.

Contributors

AJP and SCG conceived the trial and AJP is the chief investigator. AJP, PMF, DJ, MV, and TL contributed to the protocol and design of the study. SACC, SAM, LYW, AVSH, ALG, VLB, SLB, QEB, AMC, MT, AS, KD, CJW, CJAD, PJL, ECT, LF, SNF, CAG, RL, TCD, PTH, HH, DMF, VL, AM, AI, AF, CB, GK, MET, AP, EPM, AVS, AVAM, CLC, ALG, AN, SDP, KMP, ES, RKS, RT, and DPJT are study site principal investigators. PKA, EP, DJ, PMF, SB, AMM, AML, KRWE, MNR, BA, PC, SK, KJE, AL, AF, SR, PJO, SHCH, SJ, HM, JV, IH, RM, YFM, NS, RS, MDS, MEEW, TLV, RC-J, and CH contributed to the implementation of the study or data collection. MV and SF did the statistical analysis. CMG, ADD, CCDJ and RT were responsible for vaccine manufacturing. MV and AJP contributed to the preparation of the report. All authors critically reviewed and approved the final version.

Declaration of interests

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. SCG is co-founder of Vaccitech (collaborators in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines and a patent application covering this SARS-CoV-2 vaccine (PCT/GB2012/000467). TL is named as an inventor on a patent application covering this SARS-CoV-2 vaccine and was a consultant to Vaccitech for an unrelated project, during the conduct of the study. PMF is a consultant to Vaccitech during the conduct of the study. AJP is chair of the UK Department of Health and Social Care's (DHSC) Joint Committee on Vaccination & Immunisation (JCVI), but does not participate in discussions on COVID-19 vaccines, and is a member of WHO's SAGE. AJP is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this Article do not necessarily represent the views of the DHSC, JCVI, NIHR, or WHO. AVSH reports personal fees from Vaccitech, outside of the submitted work, and has a patent on ChAdOx1 licensed to Vaccitech (PCT/GB2012/000467), and might benefit from royalty income to the University of Oxford from sales of this vaccine by AstraZeneca and sublicensees. MS reports grants from NIHR and non-financial support from AstraZeneca, during the conduct of the study; and grants from Janssen, GlaxoSmithKline, Medimmune, Novavax, and MCM and grants and non-financial support from Pfizer, outside of the submitted work. CG reports personal fees from the Duke Human Vaccine Institute, outside of the submitted work. ADD reports grants and personal fees from AstraZeneca, outside of the submitted work. AF is a member of the JCVI and chair of the WHO European Technical Advisory Group of Experts. AF declares research grants from Pfizer, GlaxoSmithKline, Sanofi, Merck Sharp & Dohme, and Valneva, outside of the submitted work. JV, TLV, and IH are employees of AstraZeneca. The other authors declare no competing interests.

Data sharing

Anonymised participant data will be made available when the trials are complete, upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from the end of the trial.

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FACT SHEET FOR VACCINE RECIPIENT

APPROVED FOR RESTRICTED USE IN EMERGENCY SITUATION OF ChAdOx1 nCoV- 19 CORONA VIRUS VACCINE (RECOMBINANT) COVISHIELD™ IN PREVENTION OF COVID-19 DISEASE IN INDIVIDUALS 18 YEARS OF AGE AND OLDER

This vaccine has been given restricted use license for emergency situation. It does not have a marketing authorization, however, this approval for the restricted use in emergency situation grants permission for the vaccine to be used for active immunization of individuals aged 18 years and older for the prevention of coronavirus disease 2019 (COVID-19).

Reporting of side effects

As with any new medicine, this vaccine will be closely monitored to allow quick identification of new safety information. You can help by reporting any side effects you may get after vaccination to the Serum Institute of India Pvt Ltd who is the manufacturer of COVISHIELD™ vaccine on 24x7 Toll-Free Number: +91-1800 1200124 or at pharmacovigilance@seruminstitute.com.
For more information read this fact sheet carefully.

You are being offered the Serum Institute of India Pvt. Ltd. (SIIPL) COVISHIELD™ Vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. This Fact Sheet contains information to help you understand the risks and benefits of the COVISHIELD™ Vaccine, which you may receive because there is currently a pandemic of COVID-19 disease.

The COVISHIELD™ is a vaccine and may prevent you from getting COVID-19 disease.

Read this Fact Sheet for information about the COVISHIELD™ Vaccine. Talk to the healthcare provider if you have questions. It is your choice to receive the COVISHIELD™ Vaccine.

The COVISHIELD™ vaccination course consists of two separate doses of 0.5 mL each. The second dose should be administered between 4 to 6 weeks after the first dose. However, there is data available for administration of the second dose up to 12 weeks after the first dose from the overseas studies. .

For intramuscular (IM) injection only.

The COVISHIELD™ may not protect everyone.

WHAT YOU NEED TO KNOW BEFORE YOU GET THIS VACCINE

WHAT IS COVID-19?

COVID-19 disease is caused by a coronavirus called SARS-CoV-2. This type of coronavirus has not been seen before. You can get COVID-19 through contact with another person who has the virus. It is predominantly a respiratory illness that can affect other organs. People with COVID-19 have had a wide range of symptoms reported, ranging from mild symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include: fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; diarrhea.

WHAT IS THE SIIPL COVISHIELD™ VACCINE?

The COVISHIELD™ is approved for restricted use in emergency situation vaccine that may prevent COVID-19 disease in individuals 18 years of age and older.

WHAT SHOULD YOU MENTION TO YOUR HEALTHCARE PROVIDER BEFORE YOU GET COVISHIELD™ VACCINE?

Tell the healthcare provider about all of your medical conditions, including:

- If you have ever had a severe allergic reaction (anaphylaxis) after any drug, food, any vaccine or any ingredients of COVISHIELD™ vaccine
- If you have fever
- If you have a bleeding disorder or are on a blood thinner
- If you are immunocompromised or are on a medicine that affects your immune system
- If you are pregnant or plan to become pregnant
- If you are breastfeeding
- If you have received another COVID-19 vaccine

You should consult your healthcare provider before deciding to take the vaccine.

WHO SHOULD GET THE COVISHIELD™ VACCINE?

COVISHIELD™ Vaccine has been approved for restricted use in emergency situation in individuals 18 years of age and older.

WHO SHOULD <u>NOT</u> GET THE COVISHIELD™ VACCINE?

You should not get the COVISHIELD™ Vaccine if you:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine.

WHAT ARE THE INGREDIENTS IN THE COVISHIELD™ VACCINE?

The COVISHIELD™ Vaccine includes the following ingredients:

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate (EDTA)
Water for injection

HOW IS THE COVISHIELD™ GIVEN?

The COVISHIELD™ Vaccine will be given to you as an intramuscular (IM) injection only, preferably in the deltoid muscle.

The COVISHIELD™ vaccination course consists of two separate doses of 0.5 mL each.
If you receive one dose of the COVISHIELD™ vaccine, then the second dose should be administered between 4 to 6 weeks after the first dose. However, there is data available for administration of the second dose up to 12 weeks after the first dose from the overseas studies.

If you miss your second dose
If you forget to go back at the scheduled time, ask your healthcare provider for advice. It is important that you return for your second dose of COVISHIELD™ vaccine.

HAS THE COVISHIELD™ VACCINE BEEN USED BEFORE?

The **COVISHIELD™** is used in clinical trials, a number of participants received one or two doses in overseas and Indian trials**.**

WHAT ARE THE BENEFITS OF THE COVISHIELD™ VACCINE?

In ongoing clinical trials, the **COVISHIELD™** Vaccine has been shown to prevent COVID-19 disease following 2 doses given between 4 and 12 weeks apart. The duration of protection against COVID-19 disease is currently unknown.
You may get protective immune response 4 weeks after the second dose of **COVISHIELD™** vaccine.

WHAT ARE THE RISKS OF THE COVISHIELD™ VACCINE?

Side effects that have been reported with the COVISHIELD™ Vaccine include:

Very Common (may affect more than 1 in 10 people)

- tenderness, pain, warmth, redness, itching, swelling or bruising where the injection is given
- generally feeling unwell
- feeling tired (fatigue)
- chills or feeling feverish
- headache
- feeling sick (nausea)
- joint pain or muscle ache

Common (may affect up to 1 in 10 people)

- a lump at the injection site
- fever
- being sick (vomiting)
- flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills

Uncommon (may affect up to 1 in 100 people)

- feeling dizzy
- decreased appetite
- abdominal pain
- enlarged lymph nodes
- excessive sweating, itchy skin or rash

These may not be all the possible side effects of the COVISHIELD™ Vaccine. Serious and unexpected side effects may occur. **COVISHIELD™ Vaccine is still being studied in clinical trials.**

WHAT SHOULD I DO ABOUT SIDE EFFECTS?

If you experience a severe allergic reaction, call or go to the nearest hospital.

Call the healthcare provider if you have any side effects that bother you or do not go away.

In addition, you can report side effects after vaccination to Serum Institute of India Pvt Ltd who is the manufacturer of COVISHIELD™ vaccine as below.

- 24x7 Call Center Toll-Free Number (For Medical and Adverse Event Related Queries Only): +91-1800 1200124
- pharmacovigilance@seruminstitute.com

WHAT IF I DECIDE NOT TO GET THE COVISHIELD™ VACCINE?

It is your choice to receive or not receive the COVISHIELD™ Vaccine. You may prefer to consult your healthcare provider.

CAN I RECEIVE THE COVISHIELD™ VACCINE WITH OTHER VACCINES?

There is no information on the use of the COVISHIELD™ Vaccine with other vaccines.

WHAT IF I AM PREGNANT OR BREASTFEEDING?

You may discuss your options with the healthcare provider.

WILL THE COVISHIELD™ VACCINE GIVE ME COVID-19 INFECTION?

No. The COVISHIELD™ COVID-19 Vaccine does not contain SARS-CoV-2 and cannot give you COVID-19 infection.

KEEP YOUR VACCINATION CARD

When you get your dose, please discuss with your healthcare provider regarding the option of your vaccination record on digital platform, if available.

HOW CAN I LEARN MORE?

- Ask the healthcare provider.
- Contact your local or state public health department.

Manufactured by
SERUM INSTITUTE OF INDIA PVT. LTD.
212/2, Hadapsar, Pune 411028, INDIA

Marketed by:
SERUM INSTITUTE LIFE SCIENCES PVT. LTD.
401, Sarosh Bhavan, 16-B/1, Dr. Ambedkar Road, Pune - 411 001, INDIA

Revised: 01 January 2021

Trademark under registration

SUMMARY OF PRODUCT CHARACTERISTICS

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

COVISHIELD™

1 NAME OF THE MEDICINAL PRODUCT

COVISHIELD™

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) 5×10^{10} viral particles (vp)
*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

Both **COVISHIELD™** (manufactured by Serum Institute of India Pvt Ltd) and COVID-19 Vaccine AstraZeneca (manufactured by AstraZeneca) are ChAdOx1 nCoV- 19 Corona Virus Vaccines (Recombinant).

3 PHARMACEUTICAL FORM

Solution for injection

The solution is colourless to slightly brown, clear to slightly opaque and particle free with a pH of 6.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COVISHIELD™ is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19).

4.2 Posology and method of administration

Posology

COVISHIELD™ vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 to 6 weeks after the first dose. However, there is data available for administration of the second dose up to 12 weeks after the first dose from the overseas studies (see section 5.1).

It is recommended that individuals who receive a first dose of **COVISHIELD™** complete the vaccination course with **COVISHIELD™** (see section 4.4).

Special populations

Elderly population
Efficacy and safety data are currently limited in individuals ≥ 65 years of age (see sections 4.8 and 5.1). No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Paediatric population
The safety and efficacy of **COVISHIELD™** in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration

COVISHIELD™ is for intramuscular (IM) injection only, preferably in the deltoid muscle.

For instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

Hypersensitivity

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Concurrent illness

As with other vaccines, administration of **COVISHIELD™** should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, **COVISHIELD™** should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen. Immunocompromised individuals may have relatively weaker immune response to the vaccine regimen.

Duration and level of protection

The duration of protection has not yet been established.

As with any vaccine, vaccination with **COVISHIELD™** may not protect all vaccine recipients (See section 5.1).

Interchangeability

No data are available on the use of ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) in persons that have previously received partial vaccine series with another COVID-19 vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of COVISHIELD™ with other vaccines has not been studied (see section 5.1)

4.6 Fertility, pregnancy and lactation

Fertility

Preliminary animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Pregnancy

There is a limited experience with the use of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) in pregnant women.

Preliminary animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition or postnatal development; definitive animal studies have not been completed yet. The full relevance of animal studies to human risk with vaccines for COVID-19 remains to be established.

Administration of **COVISHIELD™** in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding

It is unknown whether **COVISHIELD™** is excreted in human milk.

4.7 Effects on ability to drive and use machines

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Overall summary of the safety profile from the Overseas studies:

The overall safety of COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,021 received at least one dose of COVID-19 Vaccine AstraZeneca. The median duration of follow-up in the COVID-19 Vaccine AstraZeneca group was 105 days post dose 1, and 62 days post dose 2.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 90.3% were aged 18 to 64 years and 9.7% were 65 years of age or older. The majority of recipients were White (75.5%), 10.1% were Black and 3.5% were Asian; 55.8% were female and 44.2% male.

The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. By day 7 the incidence of subjects with at least one local or systemic reaction was 4% and 13%, respectively. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old).

If required, analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used to provide symptomatic relief from post-vaccination adverse reactions.

Adverse drug reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 – Adverse drug reactions

MedDRA SOC	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy[a]
Metabolism and nutrition disorders	Uncommon	Decreased appetite[a]
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting
	Uncommon	Abdominal pain[a]
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosisa, pruritisa, rash[a]
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Injection site tenderness, injection site pain, injection site warmth, injection site erythema, injection site pruritus, injection site swelling, injection site bruising[b], fatigue, malaise, pyrexia[c], chills
	Common	Injection site induration, influenza like illness[a]

a Unsolicited adverse reaction

b Injection site bruising includes injection site haematoma (uncommon, unsolicited adverse reaction)

c Pyrexia includes feverishness (very common) and fever ≥38°C (common)

Very rare events of neuroinflammatory disorders have been reported following vaccination with COVID 19 Vaccine AstraZeneca. A causal relationship has not been established.

Overall summary of the safety profile from the Indian study:

COVISHIELD™ was also safe and well tolerated in the phase II/III clinical trial in India. An interim analysis included data of all 1600 participants who received first dose [1200 in **COVISHIELD™** group, 100 in Oxford/AZ-ChAdOx1 nCoV-19 vaccine group and 300 in Placebo group]. This interim analysis includes data collected until 14 Dec 2020 of all 1600 participants who received first dose and 1577 participants who received second dose.

Demographic characteristics were generally similar among participants across the three groups. Overall, among the participants who received COVISHIELD, 87.33% were aged 18 to 59 years and 12.67% were 60 years of age or older.

Overall, the incidence of solicited reactions (injection site reactions such as pain, tenderness, redness, warmth, itch, swelling and induration; and systemic reactions include fever, chills, fatigue, malaise, headache, arthralgia and myalgia), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups. No causally related SAE was caused by the study vaccine.

4.9 Overdose

Experience of overdose is limited.

There is no specific treatment for an overdose with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

COVISHIELD™ is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Efficacy and immunogenicity data from the Overseas studies:

Clinical efficacy

Interim analysis of pooled data from COV001, COV002, COV003, and COV005

COVID-19 Vaccine AstraZeneca [ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)] has been evaluated based on an interim analysis of pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001 (NCT04324606), in healthy adults 18 to 55 years of age in the UK; a Phase II/III Study, COV002 (NCT04400838), in adults ≥18 years of age (including the elderly) in the UK; a Phase III Study, COV003 (ISRCTN89951424), in adults ≥18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV005 (NCT04444674), in adults aged 18 to 65 years of age in South Africa. The studies excluded participants with history of anaphylaxis or angioedema; severe and/or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with immunosuppression. In

studies COV001 and COV002, licensed seasonal influenza and pneumococcal vaccinations were permitted (at least 7 days before or after their study vaccine). All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.

Based on the pre-defined criteria for interim efficacy analysis, COV002 and COV003 exceeded the threshold of ≥5 virologically confirmed COVID-19 cases per study and therefore contributed to the efficacy analysis; COV001 and COV005 were excluded.

In the pooled analysis for efficacy (COV002 and COV003), participants ≥18 years of age received two doses of COVID-19 Vaccine AstraZeneca (N=5,807) or control (meningococcal vaccine or saline) (N=5,829). Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 4 to 26 weeks.

Baseline demographics were well balanced across COVID-19 Vaccine AstraZeneca and control treatment groups. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 94.1% of participants were 18 to 64 years old (with 5.9% aged 65 or older); 60.7% of subjects were female; 82.8% were White, 4.6% were Asian, and 4.4% were Black. A total of 2,070 (35.6%) participants had at least one pre-existing comorbidity (defined as a BMI ≥ 30 kg/m^2, cardiovascular disorder, respiratory disease or diabetes). At the time of interim analysis the median follow up time post-dose 1 and post-dose 2 was 132 days and 63 days, respectively.

Final determination of COVID-19 cases were made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of 131 participants had SARS-CoV-2 virologically confirmed (by nucleic acid amplification tests) COVID-19 occurring ≥15 days post second dose with at least one COVID-19 symptom (objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-CoV-2 infection. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2a).

Table 2a – COVID-19 Vaccine AstraZeneca efficacy against COVID-19*

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95.84% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
Primary (see above)	5807		5829		
COVID-19 cases		30 (0.52)		101 (1.73)	70.42 (58.84, 80.63)[a]

Hospitalisations[b]		0		5 (0.09)	
Severe disease[c]		0		1 (0.02)	-
Any dose	**10,014**		**10,000**		
COVID-19 cases after dose 1		108 (1.08)		227 (2.27)	52.69 (40.52, 62.37)[d]
Hospitalisations after dose 1[b]		2 (0.02)[e]		16 (0.16)	
Severe disease after dose 1[c]		0		2 (0.02)	

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; * This is a pooled data of LDSD + SDSD regimen with second dose given at dose intervals ranging from 4 to 12 weeks. LD – Low Dose, SD – Standard Dose.
[a] 95.84% CI; [b] WHO severity grading ≥4; [c] WHO severity grading ≥6; [d] 95% CI; [e] Two cases of hospitalisation occurred on Days 1 and 10 post vaccination.

Table 2b – COVID-19 Vaccine AstraZeneca efficacy against COVID-19

Population	**COVID-19 Vaccine AstraZeneca**		**Control**		**Vaccine efficacy % (95.84% CI)**
	N	**Number of COVID-19 cases, n (%)**	**N**	**Number of COVID-19 cases, n (%)**	
Primary analysis population					
Overall (SDSD + LDSD)	5807	30 (0.52)	5829	101 (1.73)	70.42 (58.84, 80.63)
Licensing regimen					
SDSD	4440	27 (0.61)	4455	71 (1.59)	62.10 (39.96, 76.08)
Exploratory analysis					
LDSD	1367	3 (0.22)	1374	30 (2.18)	90.05 (65.84, 97.10)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; LD = Low dose; SD = Standard dose

Table 2c - COVID-19 Vaccine AstraZeneca efficacy against COVID-19 by Dose Interval (SDSD)

Dose interval	Participants with events, n (%)		Vaccine efficacy %	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
< 6 weeks	9 / 1702 (0.53)	19 / 1698 (1.12)	53.28	(-3.21, 8.86)	0.060
6-8 weeks	5 / 562 (0.88)	9 / 521 (1.73)	51.08	(-45.57, 3.56)	0.199
9-11 weeks	9 / 1056 (0.85)	24 / 1110 (2.16)	60.55	(15.23, 81.64)	0.017
≥12 weeks	4 / 1120 (0.36)	19 / 1126 (1.69)	78.79	(37.63, 92.79)	0.005

The level of protection gained from single dose of COVID-19 Vaccine AstraZeneca was assessed in an exploratory analysis that included participants who had received one dose. Participants were censored from the analysis at the earliest time point of when they received a second dose or at 12 weeks post-dose 1. In this population, vaccine efficacy from 22 days post dose 1 was 73.00% (95% CI: 48.79; 85.76 [COVID-19 Vaccine AstraZeneca 12/7,998 vs control 44/7,982]).

Exploratory analyses showed that increased immunogenicity was associated with a longer dose interval (see *Immunogenicity* Table 3). Efficacy is currently demonstrated with more certainty for dose intervals from 8 to 12 weeks. and a similar trend for efficacy. Data for intervals longer than 12 weeks are limited.

Participants who had one or more comorbidities had a vaccine efficacy of 73.43% [95% CI: 48.49; 86.29]; 11 (0.53%) vs 43 (2.02%) for COVID 19 Vaccine AstraZeneca (N=2,070) and control (N=2,113), respectively; which was similar to the vaccine efficacy observed in the overall population.

The number of COVID-19 cases (2) in 660 participants ≥ 65 years old were too few to draw conclusions on efficacy. However, in this subpopulation, immunogenicity data are available, see below.

Immunogenicity

Following vaccination with COVID-19 Vaccine AstraZeneca, in participants who were seronegative at baseline, seroconversion (as measured by a ≥4 fold increase from baseline in S-binding antibodies) was demonstrated in ≥98% of participants at 28 days after the first dose and >99% at 28 days after the second. Higher S-binding antibodies were observed with increasing dose interval (Table 3).

Generally similar trends were observed between analyses of neutralising antibodies and S-binding antibodies. An immunological correlate of protection has not been established; therefore, the level of immune response that provides protection against COVID-19 is unknown.

Table 3 – SARS CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca[a,b]

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
Overall	(N=882) 57.18 (52.8, 62.0)	(N=817) 8386.46 (7758.6, 9065.1)	(N=819) 29034.74 (27118.2, 31086.7)
Dose Interval			
<6 weeks	(N=481) 60.51 (54.1, 67.7)	(N=479) 8734.08 (7883.1, 9676.9)	(N=443) 22222.73 (20360.50, 24255.3)
6-8 weeks	(N=137) 58.02 (46.3, 72.6)	(N=99) 7295.54 (5857.4, 9086.7)	(N=116) 24363.10 (20088.5, 29547.3)
9-11 weeks	(N=110) 48.79 (39.6, 60.1)	(N=87) 7492.98 (5885.1, 9540.2)	(N=106) 34754.10 (30287.2, 39879.8)
≥12 weeks	(N=154) 52.98 (44.4, 63.2)	(N=152) 8618.17 (7195.4, 10322.3)	(N=154) 63181.59 (55180.1, 72343.4)

N = Number of subjects included in each group; GMT = Geometric mean titre; CI = Confidence interval; S = Spike

[a] Immune response evaluated using a multiplex immunoassay. [b] in individuals who received two recommended doses of vaccine.

The immune response observed in participants with one or more comorbidities was consistent with the overall population.

High seroconversion rates were observed in older adults (≥65 years) after the first (97.8% [N=136, 95% CI: 93.7; 99.5]) and the second recommended dose (100.0% [N=111, 95% CI: 96.7; NE]). The increase in S-binding antibodies was numerically lower for participants ≥65 years old (28 days after second dose: GMT=20,727.02 [N=116, 95% CI: 17,646.6; 24,345.2]) when compared to participants aged 18-64 years (28 days after second dose: GMT=30,695.30 [N=703, 95% CI: 28,496.2; 33,064.1]). The majority of participants ≥65 years old had a dose interval of <6 weeks, which may have contributed to the numerically lower titres observed.

In participants with serological evidence of prior SARS-CoV-2 infection at baseline (GMT=13,137.97 [N=29; 95% CI: 7,441.8; 23,194.1]), S-antibody titres peaked 28 days after dose 1 (GMT=175,120.84 [N=28; 95% CI: 120,096.9; 255,354.8).

Spike-specific T cell responses as measured by IFN-ɣ enzyme-linked immunospot (ELISpot) assay are induced after a first dose of COVID-19 Vaccine AstraZeneca. These do not rise further after a second dose.

Immunogenicity data from the Indian study:

GMTs of IgG antibodies against spike (S) protein were comparable between the groups at baseline – Day 1. GMTs increased significantly after each dose of vaccine in both the groups and were comparable. There was 100% seroconversion in both the groups on Day 57. The immunogenicity data indicates that COVISHIELD is comparable in terms of anti-S IgG antibody titers and seroconversion rates to Oxford/AZ-ChAdOx1 nCoV-19 vaccine (see Tables 4 and 5).

Table 4 Summary of Anti-S IgG antibodies

Timepoint	Statistic	COVISHIELD (N=291) n (%)	Oxford/AZ-ChAdOx1 nCoV-19 (N=97) n (%)
Baseline	N	291	97
	GMT	95.4	80.7
	95% CI	(77.8, 117.0)	(59.0, 110.4)
Visit 3 – Day 29 (+14)	N	289	97
	GMT	9988.1	6738.5
	95% CI	(8395.0, 11883.7)	(4880.4, 9304.1)
Visit 4 – Day 57 (+14)	n	140	46
	GMT	33331.6	33263.6
	95% CI	(27756.0, 40027.2)	(24383.1, 45378.3)

Table 5 Summary of Proportion of Participants with Seroconversion for Anti-S IgG Antibodies

Timepoint	COVISHIELD (N=291) n (%) 95(%) CI	Oxford/AZ-ChAdOx1 nCoV-19 (N=97) n (%) 95(%) CI
Visit 3 – Day 29 (+14)	279 (96.5)	89 (91.8)
	(93.7, 98.3)	(84.4, 96.4)
Visit 4 – Day 57 (+14)	**140 (100.0)**	**46 (100.0)**
	(97.4, 100.0)	(92.3, 100.0)

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Toxicity and local tolerance studies

Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity. Animal studies into potential toxicity to reproduction and development have not yet been completed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate (EDTA)
Water for injection

(The names of inactive ingredients may vary according to geographical region)

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

6.3 Shelf-life

The expiry date of vaccine is indicated on the label and packaging.

Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +25ºC. All opened multidose vials of **COVISHIELD™** should be discarded at the end of immunization session or within six hours whichever comes first.

6.4 Special precautions for storage

Store in a refrigerator (+2ºC to +8ºC).

Do not freeze. Protect from light.

Opened multidose vial

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

COVISHIELD™ is supplied as ready for use liquid in rubber-stoppered multidose vial and single dose vial in below listed presentations

1 dose – 0.5 mL per vial
2 dose – 1.0 mL per vial
5 dose – 2.5 mL per vial
10 dose – 5.0 mL per vial
20 dose – 10 mL per vial

6.6 Instructions for use, handling and disposal

Administration

COVISHIELD™ is a colourless to slightly brown, clear to slightly opaque solution. The vaccine should be inspected visually prior to administration and discarded if particulate matter or differences in the described appearance are observed.

Do not shake the vial.

Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly. Use a separate sterile needle and syringe for each individual. It is normal for liquid to remain in the vial after withdrawing the final dose.

The vaccine does not contain any preservative. Aseptic technique should be used for withdrawing the dose for administration.

Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2ºC and +25ºC. Discard any unused vaccine.

To facilitate the traceability of the vaccine, the name and the batch number of the administered product must be recorded for each recipient.

Disposal

COVISHIELD™ contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant (e.g. Hydrogen peroxide based disinfectants).

7 MARKETING AUTHORIZATION

Serum Institute of India Pvt. Ltd.
212/2, Hadapsar, Pune 411028, India.

Marketed by:

SERUM INSTITUTE LIFE SCIENCES PVT. LTD.
401, Sarosh Bhavan, 16-B/1, Dr. Ambedkar Road, Pune - 411 001, INDIA

8 MARKETING AUTHORISATION NUMBER (S)

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Trademark under registration

Title	Artwork Format		
Format No.	2002-0001-F0003-000		
Effective Date	09/11/2020	Page No.	1 of 1

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant)

COVISHIELD©

1 NAME OF THE MEDICINAL PRODUCT

COVISHIELD™
ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) contains:
ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) 5×10^{10} ** viral particles (vp)

*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

This product contains genetically modified organisms (GMOs).

For the full list of excipients, see section 6.1.

Both COVISHIELD™ manufactured by Serum Institute of India Pvt Ltd) and COVID-19 Vaccine AstraZeneca (manufactured by AstraZeneca) are ChAdOx1 nCoV-19 Corona Virus Vaccines (Recombinant).

3 PHARMACEUTICAL FORM

Solution for injection
The solution is colourless to slightly brown, clear to slightly opaque and particle free with a pH of 6.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COVISHIELD™ is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19).

4.2 Posology and method of administration

Posology
COVISHIELD™ vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 to 6 weeks after the first dose. However, there is data available for administration of the second dose up to 12 weeks after the first dose from the overseas studies (see section 5.1).
It is recommended that individuals who receive a first dose of COVISHIELD™ complete the vaccination course with COVISHIELD™ (see section 4.4).

Special populations
Elderly population
Efficacy and safety data are currently limited in individuals ≥ 65 years of age (see sections 4.8 and 5.1). No dosage adjustment is required in elderly individuals ≥ 65 years of age.

Paediatric population
The safety and efficacy of COVISHIELD™ in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration
COVISHIELD™ is for intramuscular (IM) injection only, preferably in the deltoid muscle.
For instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

Hypersensitivity
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Concurrent illness
As with other vaccines, administration of COVISHIELD™ should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders
As with other intramuscular injections, COVISHIELD™ should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals
It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen. Immunocompromised individuals may have relatively weaker immune response to the vaccine regimen.

Duration and level of protection
The duration of protection has not yet been established.
As with any vaccine, vaccination with COVISHIELD™ may not protect all vaccine recipients (See section 5.1).

Interchangeability
No data are available on the use of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) in persons that have previously received partial vaccine series with another COVID-19 vaccine.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Concomitant administration of COVISHIELD™ with other vaccines has not been studied (see section 5.1)

4.6 Fertility, pregnancy and lactation

Fertility
Preliminary animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Pregnancy
There is a limited experience with the use of ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) in pregnant women.
Preliminary animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition or postnatal development; definitive animal studies have not been completed yet. The full relevance of animal studies to human risk with vaccines for COVID-19 remains to be established.
Administration of COVISHIELD™ in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

Breastfeeding
It is unknown whether COVISHIELD™ is excreted in human milk.

4.7 Effects on ability to drive and use machines

ChAdOx1 nCoV- 19 Corona Virus Vaccine (Recombinant) has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Overall summary of the safety profile from the Overseas studies:
The overall safety of COVID-19 Vaccine AstraZeneca (ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)) is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥ 18 years old had been randomised and received either COVID-19 Vaccine AstraZeneca or control. Out of these, 12,021 received ≥ least one dose of COVID-19 Vaccine AstraZeneca. The median duration of follow-up in the COVID-19 Vaccine AstraZeneca group was 107 days post dose 1, and 62 days post dose 2.
Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 90.3% were aged 18 to 64 years and 9.7% were 65 years of age or older. The majority of recipients were White (75.5%), 10.1% were Black and 3.5% were Asian; 55.8% were female and 44.2% male.
The most frequently reported adverse reactions were injection site tenderness (>40%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. By day 7 the incidence of subjects with at least one local or systemic reaction was 4% and 13%, respectively. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.
Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old).
If required, analgesic and/or antipyretic medicinal products (e.g. paracetamol-containing products) may be used to provide symptomatic relief from post-vaccination adverse reactions.
Adverse drug reactions
Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1–Adverse drug reactions

MedDRA SOC	Frequency	Adverse reactions
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy[a]
Metabolism and nutrition disorders	Uncommon	Decreased appetite[a]
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting
	Uncommon	Abdominal pain[a]
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis[a], pruritus[a], rash[a]
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Injection site tenderness, injection site pain, injection site warmth, injection site erythema, injection site pruritus, injection site swelling, injection site bruising[b], fatigue, malaise, pyrexia[c], chills
	Common	Injection site induration, influenza like illness[a]

a Unsolicited adverse reaction
b Injection site bruising includes injection site haematoma (uncommon, unsolicited adverse reaction)
c Pyrexia includes fever/chills (very common) and fever ≥38°C (common)

Very rare events of neuroinflammatory disorders have been reported following vaccination with COVID 19 Vaccine AstraZeneca. A causal relationship has not been established.

Overall summary of the safety profile from the Indian study:
COVISHIELD™ was also safe and well tolerated in the phase II/III clinical trial in India. An interim analysis included data of all 1600 participants who received first dose (1200 in COVISHIELD™ group, 400 in Control AZ-ChAdOx1 nCoV-19 vaccine group and 300 in Placebo group). This interim analysis includes data collected until 14 Dec 2020 of all 1600 participants who received first dose and 1577 participants who received second dose.
Demographic characteristics were generally similar among participants across the three groups. Overall, among the participants who received COVISHIELD™, 87.33% were aged 18 to 59 years and 12.67% were 60 years of age or older.
Overall, the incidence of solicited reactions (injection site reactions such as pain, tenderness, redness, warmth, itch, swelling and induration; and systemic reactions include fever, chills, fatigue, malaise, headache, arthralgia and myalgia), unsolicited adverse events and serious adverse events (SAEs) was comparable in the study and control groups. No causally related SAE was caused by the study vaccine.

4.9 Overdose

Experience of overdose is limited.
There is no specific treatment for an overdose with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant). In the event of an overdose, the individual should be monitored and provided with symptomatic treatment as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
COVISHIELD™ is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Efficacy and immunogenicity data from the Overseas studies:
Clinical efficacy
Interim analysis of pooled data from COV001, COV002, COV003, and COV005
COVID-19 Vaccine AstraZeneca (ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)) has been evaluated based on an interim analysis of pooled data from four on-going randomised, blinded, controlled trials: a Phase I/II Study, COV001 (NCT04324606), in healthy adults 18 to 55 years of age in the UK; a Phase II/III Study, COV002 (ISRCTN89951424), in adults ≥18 years of age (including the elderly) in Brazil; and a Phase I/II study, COV003 (ISRCTN89951424), in adults aged 18 to 65 years of age in South Africa. The studies excluded participants with history of anaphylaxis or angioedema; severe and or uncontrolled cardiovascular, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illnesses; as well as those with immunosuppression. In studies COV001 and COV002, licensed seasonal influenza and pneumococcal vaccinations were permitted (at least 7 days before or after their study vaccine). All participants are planned to be followed for up to 12 months, for assessments of safety and efficacy against COVID-19 disease.
Based on the pre-defined criteria for interim efficacy analysis, COV002 and COV003 exceeded the threshold of ≥5 virologically confirmed COVID-19 cases per study and therefore contributed to the efficacy analysis: COV001 and COV005 were excluded.
In the pooled analysis for efficacy (COV002 and COV003), participants ≥18 years of age received two doses of COVID-19 Vaccine AstraZeneca (N=5,807) or control (meningococcal vaccine or saline) (N=5,829). Because of logistical constraints, the interval between dose 1 and dose 2 ranged from 4 to 26 weeks.
Baseline demographics were well balanced across COVID-19 Vaccine AstraZeneca and control treatment groups. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 94.1% of participants were 18 to 64 years old (with 5.9% aged 65 or older); 60.7% of subjects were female; 82.8% were White, 4.6% were Asian, and 4.4% were Black. A total of 2,070 (35.6%) participants had at least one pre-existing comorbidity defined as a BMI ≥ 30 kg/m2, cardiovascular disorder, respiratory disease or diabetes). At the time of interim analysis the median follow up time post-dose 1 and post-dose 2 was 132 days and 43 days, respectively.
Final determination of COVID-19 cases were made by an adjudication committee, who also assigned disease severity according to the WHO clinical progression scale. A total of 131 participants had SARS-CoV-2 virologically confirmed (by nucleic acid amplification tests) COVID-19 occurring ≥15 days post second dose with at least one COVID-19 symptom (objective fever (defined as ≥37.8°C), cough, shortness of breath, anosmia, or ageusia) and were without evidence of previous SARS-CoV-2 infection. COVID-19 Vaccine AstraZeneca significantly decreased the incidence of COVID-19 compared to control (see Table 2a).

Table 2a–COVID-19 Vaccine AstraZeneca efficacy against COVID-19[a]

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95.84% CI)
	N	Number of COVID-19 cases[b], n (%)	N	Number of COVID-19 cases[b], n (%)	
Primary (see above)	5807		5829		
COVID-19 cases		30 (0.52)		101 (1.73)	70.42 (58.84, 80.63)[c]
Hospitalisations[d]		0		5 (0.09)	
Severe disease[e]		0		1 (0.02)	
Any dose	10,014		10,000		
COVID-19 cases after dose 1		108 (1.08)		227 (2.27)	52.69 (40.32, 62.37)[f]
Hospitalisations after dose 1[d]		2 (0.02)[g]		16 (0.16)	
Severe disease after dose 1[e]		0		2 (0.02)	

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; * This is a pooled data of LD/SD + SD/SD regimen with second dose given at dose intervals ranging from 4 to 12 weeks. LD = Low Dose, SD = Standard Dose.
a 95.84% CI, b WHO severity grading ≥4; cWHO severity grading ≥6; d 95% CI, e Two cases of hospitalisation occurred on Days 1 and 10 post vaccination.

Table 2b–COVID-19 Vaccine AstraZeneca efficacy against COVID-19

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (95.84% CI)
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Primary analysis population					
Overall (SD/SD + LD/SD)	5807	30 (0.52)	5829	101 (1.73)	70.42 (58.84, 80.63)
Licensing regimen					
SD/SD	4440	27 (0.61)	4455	71 (1.59)	62.10 (39.96, 76.08)
Exploratory analysis					
LD/SD	1367	3 (0.22)	1374	30 (2.18)	90.05 (63.84, 97.10)

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; LD = Low dose; SD = Standard dose

Table 2c– COVID-19 Vaccine AstraZeneca efficacy against COVID-19 by Dose Interval (LD/SD)

Dose Interval	Participants with events, n (%)		Vaccine efficacy %	95% CI (%)	P-value
	AZD1222 n / N (%)	Control n / N (%)			
< 6 weeks	9 / 1702 (0.53)	19 / 1698 (1.12)	53.28	(-3.21, 8.86)	0.060
6-8 weeks	5 / 562 (0.88)	9 / 321 (1.73)	51.08	(-15.157, 3.56)	0.199
9-11 weeks	9 / 1056 (0.85)	24 / 1110 (2.16)	60.55	(15.23, 81.64)	0.017
≥ 12 weeks	4 / 1121 (0.36)	19 / 1126 (1.69)	78.79	(37.63, 92.79)	0.005

The level of protection gained from single dose of COVID-19 Vaccine AstraZeneca was assessed in an exploratory analysis that included participants who had received one dose. Participants were censored from the analysis at the earliest time point of when they received a second dose or at 12 weeks post-dose 1. In this population, vaccine efficacy from 22 days post dose 1 was 73.00% (95% CI: 48.79; 85.76) (COVID-19 Vaccine AstraZeneca 12/7,998 vs control 64/7,902).
Exploratory analyses showed that increased immunogenicity was associated with a longer dose interval (see Immunogenicity Table 2). Efficacy is currently demonstrated with more certainty for dose intervals from 8 to 12 weeks, and a similar trend for efficacy. Data for intervals longer than 12 weeks are limited.
Participants who had one or more comorbidities had a vaccine efficacy of 73.43% (95% CI: 48.49; 86.29); 11 (0.53%) vs 43 (2.02%) for COVID-19 Vaccine AstraZeneca (N=2,070) and control (N=2,113), respectively; which was similar to the vaccine efficacy observed in the overall population.
The number of COVID-19 cases (2) in 660 participants ≥ 65 years old were too few to draw conclusions on efficacy. However, in this subpopulation, immunogenicity data are available, see below.

Immunogenicity
Following vaccination with COVID-19 Vaccine AstraZeneca, in participants who were seronegative at baseline, seroconversion (as measured by a ≥ 4 fold increase from baseline in S-binding antibodies) was demonstrated in >98% of participants at 28 days after the first dose and >99% at 28 days after the second. Higher S-binding antibodies were observed with increasing dose interval (Table 2).
Generally similar trends were observed between analyses of neutralising antibodies and S-binding antibodies. An immunological correlate of protection has not been established; therefore, the level of immune response that provides protection against COVID-19 is unknown.

Table 3 - SARS CoV-2 S-binding antibody response to COVID-19 Vaccine AstraZeneca[a,b]

Population	Baseline	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)
Overall	(N=882) 97.18 (52.8, 62.0)	(N=817) 8386.46 (7758.6, 9065.1)	(N=819) 29034.74 (27118.2, 31086.7)
Dose Interval			
< 6 weeks	(N=481) 60.51 (54.1, 67.7)	(N=479) 8734.08 (7883.1, 9676.9)	(N=443) 22222.73 (20360.50, 24255.3)
6-8 weeks	(N=137) 58.02 (46.3, 72.6)	(N=89) 7295.54 (5857.4, 9086.7)	(N=116) 24363.10 (20088.5, 29547.3)
9-11 weeks	(N=110) 48.79 (39.6, 60.1)	(N=87) 7492.98 (5885.1, 9540.2)	(N=106) 34754.10 (30287.2, 39879.8)
≥ 12 weeks	(N=154) 57.98 (44.4, 63.2)	(N=152) 8618.17 (7195.4, 10322.3)	(N=154) 61181.99 (55180.1, 72343.4)

N = Number of subjects included in each group; GMT = Geometric mean titre; CI = Confidence Interval; S = Spike
[a]Immune response evaluated using a multiplex immunoassay. [b] In individuals who received two recommended doses of vaccine.

The immune response observed in participants with one or more comorbidities was consistent with the overall population.
High seroconversion rates were observed in older adults (≥65 years) after the first (97.8% [N=156, 95% CI: 93.7; 99.5]) and the second recommended dose (100.0% [N=111, 95% CI: 96.7; ∞]). The increase in S-binding antibodies was numerically lower for participants ≥65 years old (28 days after second dose: GMT: 22,727.0 [N=156, 95% CI: 17,648.6; 24,345.2]) when compared to participants aged 18-64 years (28 days after second dose: GMT=30,695.30 [N=703, 95% CI: 28,496.2; 33,064.1]). The majority of participants ≥65 years old had a dose interval of >8 weeks, which may have contributed to the numerically lower titres observed.
In participants with serological evidence of prior SARS-CoV-2 infection at baseline (GMT=13,137.97 [N=29; 95% CI: 7,441.8; 23,194.1]), S-antibody titres peaked 28 days after dose 1 (GMT=175, 120.84 [N=28; 95% CI: 120,096.9; 255,354.8]).
Spike-specific T cell responses as measured by IFN-γ enzyme-linked immunospot (ELISpot) assay are induced after a first dose of COVID-19 Vaccine AstraZeneca. These do not rise further after a second dose.

Immunogenicity data from the Indian study:
GMTs of IgG antibodies against spike (S) protein were comparable between the groups at baseline - Day 1. GMTs increased significantly after each dose of vaccine in both the groups and were comparable. There was 100% seroconversion in both the groups on Day 57. The immunogenicity data from the COVISHIELD is comparable in terms of anti-S IgG antibody titers and seroconversion rates to Oxford-AZ-ChAdOx1 nCoV-19 vaccine (see Tables 4 and 5).

Table 4 Summary of Anti-S IgG antibodies

Timepoint	Statistic	COVISHIELD™ (N=291) n (%)	Oxford/AZ-ChAdOx1 nCoV-19 (N=97) n (%)
Baseline	n GMT 95% CI	291 95.4 (77.8, 117.0)	97 80.7 (59.0, 110.4)
Visit 3 - Day 29 (+14)	n GMT 95% CI	289 9988.1 (8395.0, 11883.7)	97 6738.5 (4880.4, 9304.1)
Visit 4 - Day 57 (+14)	n GMT 95% CI	140 33331.6 (27756.0, 40027.2)	46 32263.0 (24383.1, 45378.3)

Table 5 Summary of Proportion of Participants with Seroconversion for Anti-S IgG Antibodies

Timepoint	COVISHIELD™ (N=291) n (%) 95(%) CI	Oxford/AZ-ChAdOx1 nCoV-19 (N=97) n (%) 95(%) CI
Visit 3 - Day 29 (+14)	279 (96.5) (93.7, 98.3)	89 (91.8) (84.4, 96.4)
Visit 4 - Day 57 (+14)	140 (100.0) (97.4, 100.00)	46 (100.0) (92.3, 100.0)

5.2 Pharmacokinetic properties
Not applicable.

5.3 Preclinical safety data

Toxicity and local tolerance studies
Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity. Animal studies into potential toxicity to reproduction and development have not yet been completed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Magnesium chloride hexahydrate
Polysorbate 80
Ethanol
Sucrose
Sodium chloride
Disodium edetate dihydrate (EDTA)
Water for injection
(The names of inactive ingredients may vary according to geographical region)

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

6.3 Shelf-life

The expiry date of vaccine is indicated on the label and packaging.
Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2°C and +25°C. All opened multidose vials of COVISHIELD™ should be discarded at the end of immunization session or within six hours whichever comes first.

6.4 Special precautions for storage

Store in a refrigerator (+2°C to +8°C).
Do not freeze. Protect from light.

Opened multidose vial
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

COVISHIELD™ is supplied as ready for use liquid in rubber-stoppered multidose vial and single dose vial in below listed presentations

1 dose - 0.5 mL per vial
2 dose - 1.0 mL per vial
5 dose - 2.5 mL per vial
10 dose - 5.0 mL per vial
20 dose - 10 mL per vial

6.6 Instructions for use, handling and disposal

Administration
COVISHIELD™ is a colourless to slightly brown, clear to slightly opaque solution. The vaccine should be inspected visually prior to administration and discarded if particulate matter or differences in the described appearance are observed.
Do not shake the vial.
Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection to be administered intramuscularly. Use a separate sterile needle and syringe for each individual. It is normal for liquid to remain in the vial after withdrawing the first dose.
The vaccine does not contain any preservative. Aseptic technique should be used for withdrawing the dose for administration.
Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2°C and +25°C. Discard any unused vaccine.
To facilitate the traceability of the vaccine, the name and the batch number of the administered product must be recorded for each recipient.

Disposal
COVISHIELD™ contains genetically modified organisms (GMOs). Any unused vaccine or waste material should be disposed of in accordance with local requirements. Spills should be disinfected with an appropriate antiviral disinfectant (e.g. Hydrogen peroxide based disinfectants).

Manufactured by:
SERUM INSTITUTE OF INDIA PVT. LTD.
212/2, Hadapsar, Pune 411 028. INDIA
Trademark under registration

Marketed by:
SERUM INSTITUTE LIFE SCIENCES PVT. LTD.
401, Samarth Bhawan, 164/1, Dr. Ambedkar Road,
Pune - 411 001, INDIA

20017462/1

Reason for issue: Dimension and text revised		Specification: Printed on bible paper 40 gsm.	
Customer: Domestic	Marketed by: SERUM INSTITUTE LIFE SCIENCES PVT. LTD.		
Product: COVISHIELD©	Pack insert	Colour: Pantone 355 C and 072 C	
Item Code number: 20017462/1	Specification No.:	Artwork made to: 100%	
Supercedes Item Code: 20017462/0		Dimensions: 240 x 530 mm	

PACKAGING DEVELOPMENT	QUALITY CONTROL	REGULATORY AFFAIRS	MEDICAL DEPARTMENT	QUALITY ASSURANCE

File Name: E:\Packaging artworks as on 090212\Artworks SII Pvt Ltd 231015\Domestic - New Design 2020\Insert\Covishield-ChAdOx1 nCoV-19 Corona Virus Vaccine Insert, Domestic - New 22122020.cdr Date: 02.01.2021

Central Drugs Standard Control Organization

Dte.GHS, Ministry of Health and Family Welfare, Government of India

FOREWORD

Good Clinical Practices For Clinical Research In India

Clinical research is the key to the discovery of latest diagnostic methods and to develop modern drugs for treatment of diseases. Good Clinical Practices (GCP) is an ethical and scientific quality standard for designing, conducting and recording trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well being of trial subjects are protected, consistent with the principles enshrined in the Declaration of Helsinki and ensures that clinical trial data are credible.

It has been widely recognized that India offers unique opportunities for conducting clinical trials in view of the large patient pool, well- trained and enthusiastic investigators and premiere medical institutes available in the country along with considerable low per patient trial cost, as compared to developed countries.

A need was, however, felt to develop our own Indian Guidelines to ensure uniform quality of clinical research throughout the country and to generate data for registration for new drugs before use in the Indian population. An Expert Committee set up by Central Drugs Standard Control Organisation (CDSCO) in consultation with clinical expert has formulated this GCP guideline for generation of clinical data on drugs.

The Drug Technical Advisory Board (DTAB), the highest technical body under D&C, Act, has endorsed adoption of this GCP guideline for streamlining the clinical studies in India.

I am confident that this guideline will be immensely useful to research institutions, investigators, institutional ethics committees and regulators in providing desired direction. The guideline would also be helpful to companies who may want to locate their clinical programme in the country.

Place: New Delhi

Dr. S.P. Agarwal,

Director General of Health Services

and Chairman, DTAB

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Good Clinical Practice Guidelines

INTRODUCTION

The history of Good Clinical Practice (GCP) statute traces back to one of the oldest enduring traditions in the history of medicine: The Hippocratic Oath. As the guiding ethical code it is primarily known for its edict to do no harm to the patient. However, the complexities of modern medicine research necessitate a more elaborate set of guidelines that address a Physician's ethical and scientific responsibilities such as obtaining informed consent or disclosing risk while involved in biomedical research.

Good Clinical Practice is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the study

him, the interest of science and society should never take precedence over considerations related to the well being of the study subject. It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek to establish two cardinal principles: protection of the rights of human subjects and authenticity of biomedical data generated.

These guidelines have been evolved with consideration of WHO, ICH, USFDA and European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India.

DEFINITIONS

Act

Wherever relevant, the Act means Drugs & Cosmetics Act 1940 (23 of 1940) and the Rules made thereunder.

Adverse Event (AE)

Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given. Also see *Serious Adverse Event*

Adverse Drug Reaction (ADR)

(a) In case of approved pharmaceutical products: A noxious and unintended response at doses normally used or tested in humans

(b) In case of new unregistered pharmaceutical products (or those products which are not yet approved for the medical condition where they are being tested): A noxious and unintended response at any dose(s)

The phrase ADR differs from AE, in case of an ADR there appears to be a reasonable possibility that the adverse event is related with the medicinal product being studied.

In clinical trials, an untoward medical occurrence seemingly caused by overdosing, abuse / dependence and interactions with other medicinal products is also considered as an ADR.

Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic). Type A reactions represent an augmentation of the pharmacological actions of a drug. They are dose-dependent and are, therefore, readily reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known pharmacology of the drug.

Audit of a Trial

A systematic verification of the study, carried out by persons not directly involved, such as:

(a) Study related activities to determine consistency with the *Protocol*

(b) Study data to ensure that there are no contradictions on *Source Documents*. The audit should also compare data on the Source Documents with the interim or final report. It should also aim to find out if practices were employed in the development of data that would impair their validity.

(c) Compliance with the adopted Standard Operating Procedures (*SOPs)*

Blinding / Masking

A method of "control experimentation" in which one or more parties involved are not informed of the treatment being given. Single blind refers to the study subject(s) being unaware, while Double blind refers to the study subject(s) and/or investigator(s), monitor

blind refers to the study subject(s) being unaware, while Double blind refers to the study subject(s) and/or investigator(s), monitor, data analyst(s) are being unaware of the treatment assigned.

Case Record Form (CRF)

A document designed in consonance with the Protocol, to record data and other information on each trial subject. The Case Record Form should be in such a form and format that allows accurate input, presentation, verification, audit and inspection of the recorded data. A CRF may be in printed or electronic format.

Clinical Trial (Clinical Study)

A systematic study of pharmaceutical products on human subjects – (whether patients or non-patient volunteers) – in order to discover or verify the clinical, pharmacological (including pharmacodynamics / pharmacokinetics), and / or adverse effects, with the object of determining their safety and / or efficacy.

Human/Clinical Pharmacology trials (Phase I)

The objective of phase I of trials is to determine the maximum tolerated dose in humans; pharmacodynamic effect, adverse reactions, if any, with their nature and intensity; and pharmacokinetic behaviour of the drug as far as possible. These studies are often carried out in healthy adult volunteers using clinical, physiological and biochemical observations. At least 2 subjects should be used on each dose.

Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centres.

Exploratory trials (Phase II)

In phase II trials a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centres and carried out by clinicians specialized on the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

Confirmatory trials (Phase III)

The purpose of these trials is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made.

Data on ADRs observed during clinical use of the drug should be reported along with a report on its efficacy in the prescribed format. The selection of clinicians for such monitoring and supply of drug to them will need approval of the licensing authority under Rule 21 of the Act.

Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, assessment of therapeutic value, treatment strategies used and safety profile. Phase IV studies should use the same scientific and ethical standards as applied in pre-marketing studies.

After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

Comparator Product

Comparator Product

A pharmaceutical product (including placebo) used as a reference in a clinical trial.

Confidentiality

Maintenance of privacy of study subjects including their personal identity and all medical information, from individuals other than those prescribed in the Protocol. *Confidentiality* also covers the prevention of disclosure of sponsor's proprietary information to unauthorised persons.

Co-Investigator

A person legally qualified to be an investigator, to whom the Investigator delegates a part of his responsibilities.

Co-ordinating Investigator

See Principal Investigator

Clinical Research Organisation (CRO)

An organisation to which the sponsor may transfer or delegate some or all of the tasks, duties and / or obligations regarding a Clinical Study. All such contractual transfers of obligations should be defined in writing. A CRO is a scientific body – commercial, academic or other.

Contract

A written, dated and signed document describing the agreement between two or more parties involved in a biomedical study, namely Investigator, Sponsor, Institution. Typically, a contract sets out delegation / distribution of responsibilities, financial arrangements and other pertinent terms. The "Protocol" may form the basis of "Contract".

Documentation

All records (including written documents, electronic, magnetic or optical records, scans, x-rays etc.) that describe or record the methods, conduct and results of the study, and the actions taken. The Documents include Protocol, copies of submissions and approvals from the office of the Drugs Controller General of India, ethics committee, investigator(s)' particulars, consent forms, monitor reports, audit certificates, relevant letters, reference ranges, raw data, completed CRFs and the final report. Also see: Essential Documents

Escape Treatment

A supplementary treatment, usually given to alleviate pain in placebo-controlled trials, to relieve the trial subject of the symptoms caused by the investigated disease in a study.

Essential Documents

The Documents that permit evaluation of the conduct of a study and the quality of the data generated. *See Appendix V.*

Ethics Committee

An independent review board or committee comprising of medical / scientific and non-medical / non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a study. The independent review provides public reassurance by objectively, independently and impartially reviewing and approving the "Protocol", the suitability of the investigator(s), facilities, methods and material to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards.

Final Report

A complete and comprehensive description of the study after its completion. It includes description of experimental and statistical methods and materials, presentation and evaluation of the results, statistical analyses and a critical ethical, statistical and clinical appraisal. The Investigator's declaration closing the study is a part of the Final Report.

Good Clinical Practice (GCP)

It is a standard for clinical studies or trials that encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies. It ensures that the studies are implemented and reported in such a manner that there is public assurance that the data are credible, accurate and that the rights, integrity and confidentiality of the subjects are protected. GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the "Investigational Product" are properly documented.

Impartial Witness

An impartial independent witness who will not be influenced in any way by those who are involved in the Clinical Trial, who assists at the informed consent process and documents the freely given oral consent by signing and dating the written confirmation of this consent.

Informed Consent

Voluntary written assent of a subject's willingness to participate in a particular study and in its documentation. The confirmation is sought only after information about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available and of the subject's rights and responsibilities has been provided to the potential subject.

Inspection

An official review/ examination conducted by regulatory authority(ies) of the documents, facilities, records and any other resources that are deemed by the authority(ies) to be related to the study. The inspection may be carried out at the site of the trial, at the sponsor's / or CRO's facilities in order to verify adherence to GCP as set out in these documents.

Institution

Any public or private medical facility where a clinical study is conducted.

Investigator

A person responsible for the conduct of the study at the trial site. Investigator is responsible for the rights, health and welfare of the study subjects. In case the study is conducted by a team of investigators at the study site then the designated leader of the team should be the Principal Investigator. Also see *Principal Investigator*, *Sub-investigator*.

Investigational Labelling

Labelling developed specifically for products involved in the study.

Investigational Product

A pharmaceutical product (including the Comparator Product) being tested or used as reference in a clinical study. An Investigational Product may be an active chemical entity or a formulated dosage form.

Investigator's Brochure

A collection of data (including justification for the proposed study) for the Investigator consisting of all the clinical as well as non-clinical information available on the Investigational Product(s) known prior to the onset of the trial. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If

to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new substantially relevant data is generated during the trial, the information in the Investigator's Brochure must be updated. *See Appendix IV*.

Monitor

A person appointed by the Sponsor or Contract Research Organisation (CRO) for monitoring and reporting the progress of the trial and for verification of data. The monitor ensures that the trial is conducted, recorded and reported in accordance with the Protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

Multi-Centric Study

A clinical trial conducted according to one single protocol in which the trial is taking place at different investigational sites, therefore carried out by more than one investigator.

Non-Clinical Study

Biomedical studies that are not performed on human subjects.

Non-Therapeutic Study

A study in which there is no anticipated direct clinical benefit to the Subject(s). Such studies, unless an exception is justified, should be conducted in patient(s) having a disease or condition for which the Investigational Product is intended. Subject(s) in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

Pharmaceutical Product(s)

Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose or is intended to modify physiological functions, and presented in a dosage form suitable for administration to humans.

Principal Investigator

The investigator who has the responsibility to co-ordinate between the different Investigators involved in a study at one site or different sites in case of a multi-center study.

Protocol

A document that states the background, objectives, rationale, design, methodology (including the methods for dealing with *AEs*, withdrawals etc.) and statistical considerations of the study. It also states the conditions under which the study shall be performed and managed.

A list of items to be included in the *Protocol* is compiled in a subsequent chapter.

The content and format of the protocol should take into consideration the adopted *SOPs,* the regulatory requirements and the guiding principles of *GCP*.

The term Protocol, unless otherwise specified, relates to the latest amended version of the document, read in conjunction with all its appendices and enclosures.

Protocol Amendment(s)

Any changes or formal clarifications appended to the protocol. All Protocol Amendments should be agreed upon and signed by the persons who were the signatories to the Protocol.

Quality Assurance (QA)

Systems and processes established to ensure that the trial is performed and the data are generated in compliance with GCP. QA is validated through in-process Quality Control and in and post-process auditing of clinical trial process as well as data.

Quality Control (QC)

The operational techniques and activities undertaken within the system of QA to verify that the requirements for quality of the trial related activities have been fulfilled. QC activities concern everybody involved with planning, conducting, monitoring, evaluating, data handling and reporting.

The objective of QC is to avoid exposure of study subjects to unnecessary risks and to avoid false conclusions being drawn from unreliable data.

Randomisation

The process of assigning study subjects to either the treatment or the control group. Randomisation gives all subjects the same chance of being in either group in order to reduce bias.

Regulatory Authority

The Drugs Controller General of India or an office nominated by him is the regulatory authority for the purpose of carrying out Clinical Trials in India. The Regulatory Authority approves the study Protocol, reviews the submitted data and conducts inspections.

Raw Data

It refers to all records or certified copies of the original clinical and laboratory findings or other activities in a clinical study necessary for the reconstruction and evaluation of the trial. Also see *Source Data.*

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

An AE or ADR that is associated with death, inpatient hospitalisation (in case the study was being conducted on out-patients), prolongation of hospitalisation (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

Schedule

Unless repugnant to the context, the Schedule means Schedule Y to the Drugs & Cosmetics Rules. (Reproduced here at Appendix II)

Source Data

Source Data

Original documents (or their verified and certified copies) necessary for evaluation of the Clinical Trial. These documents may include Study Subjects' files, recordings from automated instruments, tracings, X-Ray and other films, laboratory notes, photographic negatives, magnetic media, hospital records, clinical and office charts, Subjects' diaries, evaluation check-lists, and pharmacy dispensing records.

Sponsor

An individual or a company or an institution that takes the responsibility for the initiation, management and / or financing of a Clinical Study. An Investigator who independently initiates and takes full responsibility for a trial automatically assumes the role of a Sponsor.

Study Product

Any *Pharmaceutical Product* or *Comparator Product* used in a clinical study.

Sub-Investigator

See ***Co-Investigator***

Subject Files / Patient Files

A file containing demographic and medical information about a study subject. It includes hospital files, consultation records or special subject files allowing the authenticity of the information presented in CRF to be verified and where necessary allowing it to be completed or corrected. The conditions regulating the use and consultation of such documents must be honoured as prescribed under *Confidentiality*.

Study Subject (Subject)

An individual participating in a clinical trial as a recipient of the *Investigational Product*.

A *Study Subject* may be a healthy person volunteering in a trial or a person with a medical condition that is unrelated to the use of the *Investigational Product* or a person whose medical condition is relevant to the use of the *Investigational Product*.

Standard Operating Procedures (SOP)

Standard elaborate written instructions to achieve uniformity of performance in the management of clinical studies. SOPs provide a general framework for the efficient implementation and performance of all the functions and activities related to a particular study.

Subject Identification Code

A unique identification number / code assigned by the Investigator to each Study Subject to protect the Subject's identity. Subject Identification Code is used in lieu of the Subject's name for all matters related to the study.

Identification Code is used in lieu of the Subject's name for all matters related to the study.

Study Management

Steering, supervising, data management and verification, statistical processing and preparation of the study report.

Validation

Validation of Study: The process of proving, in accordance with the principles of Good Clinical Practice, that any procedure, process equipment, material, activity or system actually leads to the expected results

Validation of Data: The procedures carried out to ensure and prove that the data contained in the final report match the original observations. The procedure is applied to Raw Data, CRFs, computer software, printouts, statistical analyses and consumption of Study Product / Comparator Product.

PREREQUISITES FOR THE STUDY

2.1. Investigational Pharmaceutical Product:

Physical, chemical, pharmaceutical properties and the formulation of the Investigational Product must be documented to permit appropriate safety measures to be taken during the course of a study. Instructions for the storage and handling of the dosage form should be documented. Any structural similarity(ies) to the other known compounds should be mentioned.

2.2. Pre-clinical supporting data

The available pre-clinical data and clinical information on the Investigational Product should be adequate and convincing to support the proposed study.

2.3. Protocol

A well designed study relies predominantly on a thoroughly considered, well-structured and complete protocol.

2.3.1. Relevant components of Protocol

2.3.1.1. General information

a. Protocol title, protocol identifying number and date. All amendments should bear amendment number and date(s)

b. Name, address & contact numbers of the sponsor and the monitor / CRO

c. Name and title of the persons authorised to sign the protocol and the protocol amendments for the sponsor

d. Name, title, address and contact numbers of the sponsor's medical expert for the study

e. Name(s), title(s), address(es) and contact numbers of the investigator(s) who is / are responsible for conducting the study, along with their consent letter(s)

f. Name(s), address(es) and contact numbers of the institution(s) - clinical laboratories and / or other medical and technical departments along with the particulars of the head(s) of the institution(s) and the relevant department(s)

2.3.1.2. Objectives and Justification

a. Aims and objectives of the study, indicating the Phase to which the study corresponds

b. Name and description of the investigational product(s)

c. A summary of findings from non-clinical studies that potentially have clinical significance and from clinical studies that are relevant to the study

d. Summary of the known and potential risks and benefits, if any, to human subjects

e. Description of and justification for the route of administration, dosage regimen and treatment periods for the pharmaceutical product being studied and the product being used as control.

Dose-response relationships should be considered and stated.

f. A statement that the study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements

g. Description of the inclusion & exclusion criteria of the study population

h. References to the literature and data that are relevant to the study and that provide background for the study

2.3.1.3. Ethical Considerations

a. General ethical considerations related to the study

b. Description of how patients / healthy volunteers will be informed and how their consent will be obtained

c. Possible reasons for not seeking informed consent

2.3.1.4. Study design

The scientific integrity of the study and the credibility of the data from the study depend substantially on the study design. Description of the study design should include:

a. Specific statement of primary and secondary end points, if any, to be measured during the study

b. Description of the type of the study (randomised, comparative, blinded, open, placebo controlled), study design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), randomisation (method and procedure) and placebo controlled.

c. A schematic diagram of the study design, procedures and stages

d. Medications/treatments permitted (including rescue medications) and not permitted before and / or during the study

e. A description of the study treatments, dosage regimen, route of administration and the dosage form of the investigational product and the control proposed during the study

f. A description of the manner of packaging and labelling of the investigational product

g. Duration of the subject participation and a description of the sequence of all study periods including follow-up, if any

h. Proposed date of initiation of the study

i. Justification of the time-schedules e.g. in the light of how far the safety of the active ingredients, medicinal products has been tested, the time course of the disease in question

j. Discontinuation criteria for study subjects and instructions on terminating or suspending the whole study or a part of the study

k. Accountability procedures for the investigational products including the comparator product

l. Maintenance of study treatment randomisation codes and procedures for breaking codes

m. Documentation of any decoding that may occur during the study

n. Procedures for monitoring subjects' compliance

2.3.1.5. Inclusion, Exclusion and Withdrawal of Subjects

a. Subject inclusion criteria: specifications of the subjects (patients / healthy volunteers) including age, gender, ethnic groups, prognostic factors, diagnostic admission criteria etc. should be clearly mentioned where relevant.

b. Subject exclusion criteria, including an exhaustive statement on criteria for pre-admission exclusions

c. Subject withdrawal criteria (i.e. terminating investigational product treatment / study treatment) and procedures specifying – when and how to withdraw subjects from the treatment, type and timing of the data to be collected from withdrawn subjects, whether and how subjects are to be replaced and the follow-up on the withdrawn subjects

d. Statistical justification for the number of Subjects to be included in the Study

2.3.1.6. Handling of the Product(s)

a. Measures to be implemented to ensure the safe handling and storage of the pharmaceutical products.

b. System to be followed for labelling of the product(s) (code numbering etc.)

c. The label should necessarily contain the following information: the words - "For Clinical Studies only", the name or a code number of the study, name and contact numbers of the investigator, name of the institution, subject's identification code.

2.3.1.7. Assessment of Efficacy

a. Specifications of the effect parameters to be used

b. Description of how effects are measured and recorded

c. Time and periodicity of effect recording

d. Description of special analyses and / tests to be carried out (pharmacokinetic, clinical, laboratory, radiological etc.)

2.3.1.8. Assessment of Safety

a. Specifications of safety parameters

b. Methods and periodicity for assessing and recording safety parameters

c. Procedures for eliciting reports of and for recording and reporting adverse drug reactions and / or adverse events and inter-current illnesses

d. Type and duration of the follow-up of the subjects after adverse events

d. Type and duration of the follow-up of the subjects after adverse events

e. Information on establishment of the study-code, where it will be kept and when, how and by whom it can be broken in the event of an emergency

2.3.1.9. Statistics

a. Description of the statistical methods to be employed, including timing of any planned interim analysis

b. Number of study subjects needed to achieve the study objective, and statistical considerations on which the proposed number of subjects is based

c. Detailed break-up of the number of subjects planned to be enrolled at each study site (in case of multi-center studies)

d. The level of statistical significance to be used

e. Procedures for managing missing data, unused data and unauthentic data

f. Procedures for reporting any deviations from the original statistical plan (any deviations from the original statistical plan should be stated and justified in protocol and / in the final report, as appropriate)

g. Selection of the subjects to be included in the final analyses (e.g. all randomized subjects / all dosed subjects / all eligible subjects / evaluable subjects

2.3.1.10. Data handling and management

A statement should be clearly made in the protocol that "The investigator(s) / institution(s) will permit study related monitoring, audits, ethics committee review and regulatory inspection(s) providing direct access to source data / documents".

A copy of the CRF should be included in the protocol. Besides, the following details should be given:

a. Procedures for handling and processing records of effects and adverse events to the product(s) under study

b. Procedures for the keeping of patient lists and patient records for each individual taking part in the study. Records should facilitate easy identification of the individual subjects.

2.3.1.11. Quality control and quality assurance

a. A meticulous and specified plan for the various steps and procedures for the purpose of controlling and monitoring the study most effectively

b. Specifications and instructions for anticipated deviations from the protocol

c. Allocation of duties and responsibilities with-in the research team and their co-ordination

d. Instructions to staff including study description (the way the study is to be conducted and the

procedures for drug usage and administration)

e. Addresses and contact numbers etc. enabling any staff member to contact the research team at any hour

f. Considerations of confidentiality problems, if any arise

g. Quality control of methods and evaluation procedures

2.3.1.12. Finance and insurance

a. All financial aspects of conducting and reporting a study may be arranged and a budget made out.

b. Information should be available about the sources of economic support (e.g. foundations, private or public funds, sponsor / manufacturer). Likewise it should be stated how the expenditures should be distributed e.g. payment to subjects, refunding expenses of the subjects, payments for special tests, technical assistance, purchase of apparatus, possible fee to or reimbursement of the members of the research team, payment of the investigator / institution etc.)

c. The financial arrangement between the sponsor, the individual researcher(s) / manufacturer involved, institution and the investigator(s) in case such information is not stated explicitly

d. Study Subjects should be satisfactorily insured against any injury caused by the study

e. The liability of the involved parties (investigator, sponsor / manufacturer, institution(s) etc.) must be clearly agreed and stated before the start of the study

2.3.1.13. Publication policy

A publication policy, if not addressed in a separate agreement, should be described in the protocol.

2.3.1.14. Evaluation

a. A specified account for how the response is to be evaluated

b. Methods of computation and calculation of effects

c. Description of how to deal with and report subjects withdrawn from / dropped out of the study

2.3.2. Supplementaries and appendices:

The following documents should be appended with the protocol:

a. Information to the Study Subjects and the mode of providing it

b. Instructions to staff

c. Descriptions of special procedures

2.4. Ethical & Safety Considerations

2.4.1. Ethical Principles

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current revision of Declaration of Helsinki (see Appendix 1) and should respect three basic principles, namely justice, respect for persons, beneficence (to maximize benefits and to minimize harms and wrongs) and non malaficence (to do no harm) as defined by "Ethical Guidelines for Biomedical Research on Human Subjects" issued by the Indian Council of Medical Research and any other laws and regulations of the country, which ensure a greater protection for subjects.

The following principles are to be followed:

a. **Principles of essentiality** whereby, the research entailing the use of human subjects is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental well being of the planet.

b. **Principles of voluntariness, informed consent and community agreement** whereby, Study Subjects are fully apprised of the Study and the impact and risk of such Study on the Study Subjects and others; and whereby the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by them or by someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding.

c. **Principles of non-exploitation** whereby as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born.

d. **Principles of privacy and confidentiality** whereby, the identity and records of the human subjects of the research or experiment are as far as possible kept confidential; and that no details about identity of said human subjects, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the human subject concerned, or someone authorised on their behalf; and after ensuring that the said human subject does not suffer from any form of hardship, discrimination or stigmatisation as a consequence of having participated in the research or experiment.

e. **Principles of precaution and risk minimisation** whereby due care and caution is taken at all stages of the research and experiment (from its inception as a research idea, its subsequent research design, the conduct of the research or experiment and its applicative use) to ensure that the research subject and those affected by it

are put to the minimum risk, suffer from no irreversible adverse effects and, generally, benefit from and by the research or experiment.

f. **Principles of professional competence** whereby, the research is conducted at all times by competent and qualified persons, who act with total integrity and impartiality and who have been made aware of, and mindful of, the ethical considerations to be borne in mind in respect of such Study.

f. **Principles of accountability and transparency** whereby, the research or experiment will be conducted in a fair, honest, impartial and transparent manner, after full disclosure is made by those associated with the Study of each aspect of their interest in the Study, and any conflict of interest that may exist; and whereby, subject to the principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research inclusive of data and notes are retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring, evaluation of the research, conducting further research (whether by the initial researcher or otherwise) and in order to make such records available for scrutiny by the appropriate legal and administrative authority, if necessary.

h. **Principles of the maximisation of the public interest and of distributive justice** whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research subject themselves.

i. **Principles of institutional arrangements** whereby, there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.

j. **Principles of public domain** whereby, the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.

k. **Principles of totality of responsibility** whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

l. **Principles of compliance** whereby, there is a general and positive duty on all persons conducting associated

i. **Principles of compliance** whereby, there is a general and positive duty on all persons, conducting, associated or connected with any research entailing the use of a human subject to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with.

2.4.2. Ethics Committee:

The sponsor and / or investigator should seek the opinion of an independent *Ethics Committee* regarding suitability of the *Protocol*, methods and documents to be used in recruitment of *Subjects* and obtaining their *Informed Consent* including adequacy of the information being provided to the Subjects. The Ethics Committees are entrusted not only with the initial view of the proposed research protocols prior to initiation of the projects but also have a continuing responsibility of regular monitoring for the compliance of the Ethics of the approved programmes till the same are completed. Such an ongoing review is in accordance with the Declaration of Helsinki and all the international guidelines for biomedical research

2.4.2.1 Basic Responsibilities

The basic responsibility of an IEC is to ensure a competent review of all ethical aspects of the project proposals received and execute the same free from any bias and influence that could affect their objectivity.

The IECs should specify in writing the authority under which the Committee is established, membership requirements, the terms of reference, the conditions of appointment, the offices and the quorum requirements. The responsibilities of an IEC can be defined as follows :

a. To protect the dignity, rights and well being of the potential research participants.

b. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.

c. To assist in the development and the education of a research community responsive to local health care requirements

2.4.2.2. Composition

a. IEC should be multidisciplinary and multi-sectorial in composition. Independence and competence are the two hallmarks of an IEC.

b. The number of persons in an ethical committee be kept fairly small (5-7 members). It is generally accepted that a minimum of five persons is required to compose a quorum. There is no specific recommendation for a widely acceptable maximum number of persons but it should be kept in mind that too large a Committee will make it difficult in reaching consensus opinion. 12 to 15 is the maximum recommended number

c. The Chairperson of the Committee should preferably be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary who generally belongs to the same Institution should conduct the business of the Committee. Other members should be a mix of medical/non-medical, scientific and non-scientific persons including lay public to reflect the differed viewpoints. The composition may be as follows :-

1. Chairperson
2. 1-2 basic medical scientists (preferably one pharmacologists).
3. 1-2 clinicians from various Institutes
4. One legal expert or retired judge
5. One social scientist / representative of non-governmental voluntary agency
6. One philosopher / ethicist / theologian
7. One lay person from the community
8. Member Secretary

d. The ethical committee at any institution can have as its members, individuals from other institutions or communities if required. There should be adequate representation of age, gender, community; etc. in the Committee to safeguard the interests and welfare of all sections of the community/society. Members should be aware of local, social and cultural norms, as this is the most important social control mechanism. If required subject experts could be invited to offer their views.

2.4.2.3. Terms of Reference

The IEC members should be made aware of their role and responsibilities as committee members. Any change in the regulatory requirements should be brought to their attention and they should be kept abreast of all national and international developments in this regard. The Terms of References should also include a statement on Terms of Appointment with reference to the duration of the term of membership, the policy for removal, replacement and resignation procedure etc. Each Committee

should have its own operating procedures available with each member.

2.4.2.4. Review Procedures

The Ethics Committee should review every research proposal on human subjects. It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the subjects with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues. **The ethical review should be done through formal meetings and should not resort to decisions through circulation of proposals.**

2.4.2.5. Submission of Application

The researcher should submit an appropriate application to the IEC in a prescribed format along with the study protocol at least three weeks in advance. The protocol should include the following:

1. Clear research objectives and rationale for undertaking the investigation in human subjects in the light of existing knowledge.
2. Recent curriculum vitae of the Investigators indicating qualification and experience.
3. Subject recruitment procedures.
4. Inclusion and exclusion criteria for entry of subjects in the study.
5. Precise description of methodology of the proposed research, including intended dosages and routes of administration of drugs, planned duration of treatment and details of invasive procedures if any.
6. A description of plans to withdraw or withhold standard therapies in the course of research.
7. The plans for statistical analysis of the study.
8. Procedure for seeking and obtaining informed consent with sample of patient information sheet and informed consent forms in English and vernacular languages.
9. Safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory and animal research.
10. For research carrying more than minimal risk, an account of plans to provide medical therapy for such risk or injury or toxicity due to over-dosage should be included.
11. Proposed compensation and reimbursement of incidental expenses.
12. Storage and maintenance of all data collected during the trial.
13. Plans for publication of results - positive or negative - while maintaining the privacy and confidentiality of the study participants.
14. A statement on probable ethical issues and steps taken to tackle the same.
15. All other relevant documents related to the study protocol including regulatory clearances.
16. Agreement to comply with national and international GCP protocols for clinical trials.
17. Details of Funding agency / Sponsors and fund allocation for the proposed work.

2.4.2.6. Decision Making Process

The IEC should be able to provide complete and adequate review of the research proposals submitted to them It should meet periodically at frequent intervals to review new proposals, evaluate annual progress of ongoing ones and assess final reports of all research activities involving human beings through a previously scheduled agenda, amended wherever appropriate.

1. The decision must be taken by a broad consensus after the quorum requirements are fulfilled to recommend / reject / suggest modification for a repeat review or advice appropriate steps. The Member Secretary should communicate the decision in writing.

2. A member must voluntarily withdraw from the IEC while making a decision on an application which evokes a conflict of interest which should be indicated in writing to the chairperson prior to the review and should be recorded so in the minutes.

3. If one of the members has her/his own proposal for review, then the member should not participate when the project is discussed.

4. A negative decision should always be supported by clearly defined reasons.

5. An IEC may decide to reverse its positive decision on a study in the event of receiving information that may adversely affect the benefit/risk ratio.

6. The discontinuation of a trial should be ordered if the IEC finds that the goals of the trial have already been achieved midway or unequivocal results are obtained.

7. In case of premature termination of study, notification should include the reasons for termination along with the summary of results conducted till date.

8. The following circumstances require the matter to be brought to the attention of IEC :

   a. any amendment to the protocol form the originally approved protocol with proper justification;

   b. serious and unexpected adverse events and remedial steps taken to tackle them;

   c. any new information that may influence the conduct of the study.

9. If necessary, the applicant/investigator may be invited to present the protocol or offer clarifications in the meeting. Representative of the patient groups or interest groups can be invited during deliberations to offer their viewpoint.

10. Subject experts may be invited to offer their views, but should not take part in the decision making process. However, her/his opinion must be recorded.

11. Meetings are to be minuted which should be approved and signed by the Chairperson.

2.4.2.7. Interim Review

The IEC should decide and record the special circumstances and the mechanism when an interim review can be resorted-to instead of waiting for the scheduled time of the meeting. However, decisions taken should be brought to the notice of the main committee. This can be done for the following reasons:

i) re-examination of a proposal already examined by the IEC;

ii) research study of a minor nature such as examination of case records etc.;

iii) an urgent proposal of national interest.

2.4.2.8. Record Keeping

All documentation and communication of an IEC are to be dated, filed and preserved according to written procedures. Strict confidentiality is to be maintained during access and retrieval procedures. Records should be maintained for the following :

i. the Constitution and composition of the IEC;

ii. the curriculum vitae of all IEC members;

iii. standing operating procedures of the IEC;

iv. national and international guidelines;

v. copies of the Protocol, data collection formats, CRFs, investigational brochures etc. submitted for review;

vi. all correspondence with IEC members and investigators regarding application, decision and follow up;

vii. agenda of all IEC meetings;

viii. minutes of all IEC meetings with signature of the Chairperson;

ix. copies of decisions communicated to the applicants;

x. record of all notification issued for premature termination of a study with a summary of the reasons;

xi. final report of the study including microfilms, CDs and Video-recordings.

It is recommended that all records must be safely maintained after the completion / termination of the study for at least a period of 5 years if it is not possible to maintain the same permanently.

2.4.2.9. Special Considerations

While all the above requirements are applicable to biomedical research as a whole irrespective of the speciality of research, there are certain specific concerns pertaining to specialised areas of research which require additional safe guards / protection and specific considerations for the IEC to take note of. Examples of such instances are research involving children, pregnant and lactating women, vulnerable subjects and those with diminished autonomy besides issues pertaining to commercialisation of research and international collaboration. The observations and suggestions of IEC should be given in writing in unambiguous terms in such instances.

2.4.3. Informed Consent Process

2.4.3.1. **Informed Consent of Subject :**

Prior to the beginning of the Study the Investigator(s) should obtain the Ethics Committee's approval for the

written informed consent form and all information being provided to the Subjects and / or their legal representatives or guardians as well as an impartial witness.

None of the oral and written information concerning the Study, including the written informed consent form, should contain any language that causes the Subject(s) or their legal representatives or guardians to waive or to appear to waive their legal rights, or that releases or appears to release the Investigator, the Institution, the Sponsor or their representatives from their liabilities for any negligence.

The information should be given to the Subjects and / or their legal representatives or guardians in a language and at a level of complexity that is understandable to the Subject(s) in both written and oral form, whenever possible.

Subjects, their legal representatives or guardians should be given ample opportunity and time to enquire about the details of the Study and all questions answered to their satisfaction.

The Investigator(s), Sponsor or staff of the Institution should not coerce or unduly influence a potential Subject to participate or to continue to participate in the Study. Careful consideration should be given to ensuring the freedom of consent obtained from members of a group with a hierarchical structure- such as medical, pharmacy and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. Persons with incurable diseases, in nursing homes, in detention, unemployed or impoverished, in emergency rooms, homeless persons, nomads, refugees and any ethnic or racial minority groups should be considered as vulnerable population whose mode of consent should be carefully considered and approved by the Ethics Committee.

Prior to the Subject's participation in the Study the written Informed Consent form should be signed and personally dated by

1. (i) The Subject *or* (ii) if the Subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability, by the Subject's legal representative or guardian *or* (iii) if the Subject and his legal representative or guardian is unable to read / write,

2. An impartial witness who should be present during the entire informed consent discussion

3. The Investigator

By signing the consent form the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the Subject or the Subject's legal representative or the guardian, and that informed consent was freely given by the Subject or the Subject's legal representative or the guardian.

The Subject's legal representative or guardian (if the subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability), the

inclusion of such patients in the study may be acceptable if the ethics committee is in principle, in agreement, and if the investigator thinks that the participation will promote the welfare and interest of the Subject. The agreement of a legal representative or the guardian that participation will promote the welfare and interest of the Subject should also be recorded with dated signature. If, however, neither the signed Informed Consent nor the witnessed signed verbal consent are possible – this fact must be documented stating reasons by the Investigator and also brought to the knowledge of Ethics Committee without any delay.

2.4.3.2. **Essential information for prospective research on subjects :** Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information in the language he or she is able to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural context :

i. the aims and methods of the research;

ii. the expected duration of the subject participation;

iii. the benefits that might reasonably be expected as an outcome of research to the subject or to others;

iv. any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment to which she/he is being subjected;

v. any foreseeable risk or discomfort to the subject resulting from participation in the study;

vi. right to prevent use of his/her biological sample (DNA, cell-line, etc.) at any time during the conduct of the research;

vii. the extent to which confidentiality of records could be able to safeguard, confidentiality and the anticipated consequences of breach of confidentiality;

viii. free treatment for research related injury by the investigator / institution;

ix. compensation of subjects for disability or death resulting from such injury;

x. freedom of individual / family to participate and to withdraw from research any time without penalty or loss of benefits which the subject would otherwise be entitled to;

xi. the identity of the research teams and contact persons with address and phone numbers;

xii. foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same;

xiii. risk of discovery of biologically sensitive information;

xiv. publication, if any, including photographs and pedigree charts.

The quality of the consent of certain social groups requires careful consideration as their agreement to volunteer may be unduly influenced by the Investigator.

2.4.3.3. Informed Consent in Non-Therapeutic Study :

In case of a Non-Therapeutic Study the consent must always be given by the subject. Non-Therapeutic Studies may be conducted in subjects with consent of a legal representative or guardian provided all of the following conditions are fulfilled:

1. The objective of the Study can not be met by means of a trial in Subject(s) who can personally give the informed consent
2. The foreseeable risks to the Subject(s) are low
3. Ethics Committee's written approval is expressly sought on the inclusion of such Subject(s)

2.4.4. Essential Information on Confidentiality for Prospective Research Subjects

Safeguarding confidentiality **-** The investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual subjects. Data of individual subjects can be disclosed only in a court of law under the orders of the presiding judge or in some cases may be required to communicate to drug registration authority or to health authority. Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed.

2.4.5. Compensation for Participation

Subjects may be paid for the inconvenience and time present, and should be reimbursed for expenses incurred, in connection with their participation in research. They may also receive free medical services. However, payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in research against their better judgement (inducement). All payments, reimbursement and medical services to be provided to research subjects should be approved by the IEC. Care should be taken :

i. when a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses;

ii. when a subject is withdrawn from research for medical reasons related to the study the subject should get the benefit for full participation;

iii. when a subject withdraws for any other reasons he/she should be paid in proportion to the amount of participation.

Academic institutions conducting research in alliance with industries / commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilities of researchers and business interests (e.g. ownership or part-ownership of a company developing a new product). In cases where the review board/committee determines that a conflict of interest may damage the scientific integrity of a project or cause harm to research participants, the board should advise accordingly. Institutions need self-regulatory processes to monitor, prevent and resolve such conflicts of interest. Prospective participants in research should also be informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research. Undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of

health care reimbursement, costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes.

2.4.6. Selection of Special Groups As Research Subject

2.4.6.1. Pregnant or nursing women :

Pregnant or nursing women should in no circumstances be the subject of any research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about the foetus, pregnancy and lactation. As a general rule, pregnant or nursing women should not be subjects of any clinical trial except such trials as are designed to protect or advance the health of pregnant or nursing women or foetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable subjects.

a. The justification of participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits. Example of such trials are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, trials for detecting fetal abnormalities and for conditions associated with or aggravated by pregnancy etc. Women should not be encouraged to discontinue nursing for the sake of participation in research and in case she decides to do so, harm of cessation of breast feeding to the nursing child should be properly assessed except in those studies where breast feeding is harmful to the infant.

b. Research related to termination of pregnancy: Pregnant women who desire to undergo Medical Termination of Pregnancy (MTP) could be made subjects for such research as per The Medical Termination of Pregnancy Act, GOI, 1971.

c. Research related to pre-natal diagnostic techniques: In pregnant women such research should be limited to detect the foetal abnormalities or genetic disorders as per the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, GOI, 1994 and not for sex determination of the foetus.

2.4.6.2. Children:

Before undertaking trial in children the investigator must ensure that -

a. children will not be involved in research that could be carried out equally well with adults;

b. the purpose of the research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children;

c. a parent or legal guardian of each child has given proxy consent;

d. the assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors, adolescents etc;

e. research should be conducted in settings in which the child and parent can obtain adequate medical and psychological support;

f. interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child subject must be justified in relation to anticipated risks involved in the study and anticipated benefits to society;

g. the child's refusal to participate in research must always be respected unless there is no medically acceptable alternative to the therapy provided/tested, provided the consent has been obtained from parents/guardian;

h. interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child subject as any available alternative interventions;

i. the risk presented by interventions not intended to benefit the individual child subject is low when compared to the importance of the knowledge that is to be gained.

2.4.6.3. Vulnerable groups :

Effort may be made to ensure that individuals or communities invited for research be selected in such a way that the burdens and benefits of the research are equally distributed.

a. research on genetics should not lead to racial inequalities;

b. persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them;

c. rights and welfare of mentally challenged and mentally differently able persons who are incapable of giving informed consent or those with behavioral disorders must be protected.

d. Adequate justification is required for the involvement of subjects such as prisoners, students, subordinates, employees, service personnel etc. who have reduced autonomy as research subjects.

2.4.7. Compensation for Accidental Injury

Research subjects who suffer physical injury as a result of their participation in the Clinical Trial are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability subject to confirmation from IEC In case of death, their dependents are entitled to material compensation.

2.4.7.1. Obligation of the sponsor to pay **:**

The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any serious sphysical or mental injury for which subjects are entitled to compensation or agree to provide insurance coverage for an unforeseen injury whenever possible.

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RESPONSIBILITIES

3.1. Sponsor:

3.1.1. Investigator and Institution Selection:

The Sponsor is responsible for selecting the Investigator(s) / Institutions taking into account the appropriateness and availability of the study site and facilities. The Sponsor must assure itself of the Investigator's qualifications and availability for the entire duration of the Study. If organisation of a co-ordinating committee and / or selection of co-ordinating investigators are to be utilised in multi-centric studies their organisation and / or selection are Sponsor's responsibilities.

Before entering an agreement with an Investigator(s) / Institution(s) to conduct a Study, the Sponsor should provide the Investigator(s) / Institution(s) with the Protocol and an up-to-date Investigator's Brochure. Sponsor should provide sufficient time to review the Protocol and the information provided in the Investigator's Brochure.

3.1.2. Contract

The Sponsor should enter into a formal and legal agreement / contract with the Investigator(s) / Institution(s) on the following terms:

a. To conduct the Study in compliance with GCP, the applicable regulatory requirements and the Protocol agreed to by the Sponsor and given approval / favourable opinion by the Ethics Committee

b. To comply with the procedures for data recording, and reporting

c. To permit monitoring, auditing and inspection

d. To retain the study related essential documents until the Sponsor informs the Investigator(s) / Institution(s) in

d. To retain the study related essential documents until the Sponsor informs the Investigator(s) / Institution(s) in writing that these documents are no longer needed

The agreement should define the relationship between the investigator and the sponsor in matters such as financial support, fees, honorarium, payments in kind etc.

3.1.3. SOP

The Sponsor should establish detailed Standard Operating Procedures (SOP's). The Sponsor and the Investigator(s) should sign a copy of the Protocol and the SOPs or an alternative document to confirm their agreement.

3.1.4. Allocation of duties and responsibilities:

Prior to initiating a Study the Sponsor should define and allocate all Study related duties and responsibilities to the respective identified person(s) / organisation(s).

3.1.5. Study management, data handling and record keeping:

The Sponsor is responsible for securing agreement with all involved parties on the allocation of Protocol related and other responsibilities like:

a. Access to all Study related sites, source data / documents and reports for the purpose of inspection, monitoring and auditing by the authorised parties and inspection by national and foreign regulatory authorities

b. Data processing

c. Breaking of the Code

d. Statistical analysis

e. Preparation of the Study Report

f. Preparation and submission of materials to the Ethics Committee, Regulatory Authorities and any other review bodies

g. Reporting the ADRs, AEs to the Ethics Committee

h. Quality Assurance and Quality Control systems with written SOPs to ensure that the Study is conducted and data are generated, documented (recorded), and reported – in compliance with the Protocol, GCP and the applicable regulatory requirement(s)

It shall be the responsibility of sponsor to make arrangements for safe and secure custody of all study related documents and material for a period of three years after the completion of the study or submission of the data to

the regulatory authority(ies) whichever is later.

The Sponsor may consider establishing an Independent Data Monitoring Committee (IDMC) to assess the progress of the Study. This includes the safety data and the critical efficacy endpoints at various intervals, and to recommend to the Sponsor whether to continue, modify, or stop a Study. The IDMC should have written operating procedures and should maintain written records of all its meetings.

3.1.6. Compensation for Participation

Subjects may be paid compensation for participation in accordance with the guidelines listed in 2.4.5.

3.1.7. Confirmation of review by the Ethics Committee

The Sponsor shall obtain from the Investigator(s) and / or the Institutions

a. The particulars about the members of the Investigator's / Institution's Ethics Committee including their names, addresses, qualifications and experience

b. An undertaking that the Ethics Committee is organised and operates according to the GCP and the applicable laws and regulations

c. Documented approval / favourable opinion of the Ethics Committee before the initiation of the Study

d. A copy of the recommendations in case the Ethics Committee conditions its approval upon change(s) in any aspect of the Study such as modification(s) of the Protocol, written Informed Consent Form, any other written information *and / or* other procedures

e. Ethics Committee's documents relating to re-evaluations / re-approvals with favourable opinion, and of any withdrawals or suspensions of approval / favourable opinion

3.1.8. Information on Investigational Products

As a prerequisite to planning of a Study, the Sponsor is responsible for providing the Investigator(s) with an Investigator's Brochure. The Brochure must contain the available chemical, pharmaceutical, toxicological, pharmacological and clinical data including the available data from previous and ongoing clinical studies regarding the Investigational Product and, where appropriate, the Comparator Product. This information should be accurate and adequate to justify the nature, scale and the duration of the Study. In addition, the Sponsor must bring any relevant new information arising during the period of Study to the attention of the Investigator(s) as well as the Ethics Committee.

3.1.9. Supply, storage and handling of Pharmaceutical Products

The Sponsor is responsible for supplying the Investigational Product's, including Comparator(s) and Placebo if applicable. The Products should be manufactured in accordance with the principles of GMPs and they should be suitably packaged in the manner that will protect the product from deterioration and safeguard blinding procedures (if applicable) and should be affixed with appropriate investigational labelling

(if applicable) and should be affixed with appropriate investigational labelling.

The Sponsor should determine the Investigational Product's acceptable storage conditions, reconstitution procedures and devices for product infusions if any, and communicate them in writing to all involved parties, besides stating them on the Product labels where ever possible.

In case any significant formulation changes are made in the Investigational Product during the course of the Study - the results of any additional studies of the new formulation (e.g. stability, bioavailability, dissolution rate) should be provided to the involved parties to enable them to determine their effects on the pharmacokinetic profile of the Product prior to the use in the Study.

The Sponsor should not supply an Investigator / Institution with the Product until the Sponsor obtains all required documentation (e.g. approval / favourable opinion from Ethics Committee and Regulatory Authorities).

The Sponsor should document procedures and lay down responsibilities for

a. adequate and safe receipt, handling, storage, dispensing of the Product

b. retrieval of unused Product from the Subjects and

c. return of unused Product to the Sponsor (or its alternative disposal procedure).

Sponsor should maintain records for retrieval of Product (e.g. retrieval after study completion, expired product retrieval etc.).

Sponsor should also maintain records of the quantities of Investigational Product with proper batch numbers. The Sponsor should ensure that the Investigator is able to establish a system within his / her Institution for proper management of the Products as per the procedures.

The Sponsor should maintain sufficient samples from each batch and keep the record of their analyses and characteristics for reference, so that if necessary an independent laboratory may be able to recheck the same.

3.1.10. Safety Information:

Sponsor is responsible for the ongoing safety evaluation of the Product. The Sponsor should promptly notify all concerned of findings that could adversely affect the safety of the Subjects, impact the conduct of the Study or alter the Ethics Committee's approval / favourable opinion to continue the Study. The Sponsor, together with Investigator(s), should take appropriate measures necessary to safeguard the study subjects.

3.1.11. Adverse Drug Reaction Reporting:

The Sponsor should provide ADR / AE reporting forms to the Investigator(s) / Institution(s). The Sponsor should expedite the reporting to all concerned (including the Ethics Committee and the regulatory authorities) of all serious and/or unexpected adverse drug reactions.

3.1.12. Study Reports:

The Sponsor should ensure the preparation and appropriate approval(s) of a comprehensive final clinical study report suitable for regulatory and / or marketing purposes, whether or not the study has been completed. All reports prepared should meet the standards of the GCP guidelines for Format and Content of Clinical Study Reports. The sponsor should also submit any safety updates and / or periodic reports as prescribed by the regulatory authorities.

3.1.13. Monitoring

Although an extensively written guidance can assure appropriate conduct of the study, the sponsor should ensure that the studies are adequately monitored. The determination of the extent and the nature of monitoring should be based on considerations such as objective, purpose, design, complexity, blinding, size and endpoints of the study. The sponsor must appoint adequately trained monitors or CRO to supervise an ongoing study.

3.1.14. Audit:

Sponsor should perform an audit as a part of QA system. This audit should be conducted with the purpose of being independent and separate from routine monitoring or quality control functions. Audit should evaluate the study conduct and compliance with the protocol, SOPs, GCPs and applicable regulatory requirements. For the purpose of carrying out the audit – the sponsor may appoint individuals qualified by training and experience to conduct audits. The Auditors should be independent of the parties involved in the study and their qualifications should be documented.

The Sponsor should ensure that the auditing is conducted in accordance with the Sponsor's SOPs on what to audit, how to audit, the frequency of audit and the form & content of audit reports. Auditors should document their observations which should be archived by the Sponsors and made available to the Regulatory Authorities when called for.

Sponsor should initiate prompt action in case it is discovered that any party involved has not entirely complied with the GCP, SOPs, Protocol and / or any applicable regulatory requirements. If monitoring / auditing identifies serious and / or persistent non-compliance - the Sponsor should terminate the defaulting party's participation in the study and promptly notify to the regulatory authority.

3.1.15. Multicentre Studies

Since multicentre studies are conducted simultaneously by several investigators at different institutions following the same protocol, the sponsor should make special administrative arrangements for their conduct. These

administrative arrangements should provide adequate assurance that the study will be planned and conducted according to GCPs.

The various tasks that may need special consideration include responsibility for commencement and overall performance of the study, supervision of the data, monitoring of the ADRs / AEs and various other policy matters. The functions, responsibilities and mandate of any special committee(s) set up or person(s) should be described in the study protocol, along with the procedure for their nomination.

A co-ordinating committee may be set up or a co-ordinator appointed with responsibility for the control of practical performance and progress of the study and maintaining contact with the regulatory authorities and the ethics committee(s).

Ideally, the studies should begin and end simultaneously at all institutions.

The sponsor should make arrangements to facilitate the communication between investigators at various sites. All investigators and other specialists should be given the training to follow the same protocol and systems. The sponsor should obtain written acceptance of the protocol and its annexes from each of the investigator and institution involved.

The CRFs should be so designed as to record the required data at all multicentre sites. For those investigators who are collecting additional data, supplemental CRFs should be provided to record the additional data.

Before initiation of multi-centre studies the sponsor should carefully define and document the following:

a. ethics committee(s), and the number of ethics committees to be consulted

b. role and responsibilities of the co-ordinating investigators

c. role and responsibilities of the CRO

d. randomisation procedure

e. standardisation and validation of methods of evaluation and analyses of laboratory and diagnostic data at various centres

f. structure and function of a centralised data management set-up

3.1.16. Premature Termination or Suspension of a Study

In case the sponsor chooses to or is required to terminate prematurely or suspend the study, then the sponsor should notify the investigator(s), institution(s), the ethics committee and the regulatory authorities accordingly. The notification should document the reason(s) for the termination or suspension by the sponsor or by the investigator / institution.

3.1.17. Role of Foreign Sponsor

If the sponsor is a foreign company, organisation or person(s) – it shall appoint a local representative or CRO to fulfil the appropriate local responsibilities as governed by the national regulations. The Sponsor may transfer any or all of the Sponsor's study related duties and functions to a CRO but the ultimate responsibility for the quality and the integrity of the Study Data shall always reside with the Sponsor. Any Study related duty, function or responsibility transferred to and assumed by a local representative or a CRO should be specified in writing. Any Study related duties, functions or responsibilities not specifically transferred to and assumed by a CRO or a local representative shall be deemed to have been retained by the Sponsor. The sponsor should utilise the services of qualified individuals e.g. bio-statisticians, clinical pharmacologists, and physicians, as appropriate, throughout all stages of the study process, from designing the protocol and CRFs and planning the analyses to analysing and preparing interim and final clinical study reports.

3.2. The Monitor:

The monitor is the principal communication link between the sponsor and the investigator and is appointed by the sponsor.

3.2.1. Qualifications

The monitor should have adequate medical, pharmaceutical and / or scientific qualifications and clinical trial experience. Monitor should be fully aware of all the aspects of the product under investigation and the protocol (including its annexes and amendments).

3.2.2. Responsibility

The main responsibility of the monitor is to oversee the progress of the study and to ensure that the study conduct and data handling comply with the protocol, GCPs and applicable ethical and regulatory requirements.

(a) The Monitor should verify that the investigator(s) have the adequate qualifications, expertise and the resources to carry out the study. Monitor should also confirm that the investigator(s) shall be available throughout the study period.

(b) Monitor should ascertain that the institutional facilities like laboratories, equipment, staff, storage space etc. are adequate for safe and proper conduct of the study and that they will remain available throughout the study.

(c) The Monitor should verify (and wherever necessary make provisions to ensure) that

1. the investigational product(s) are sufficiently available throughout the study and is stored properly
2. the investigational product(s) are supplied only to subjects who are eligible to receive it and at the

2. the investigational product(s) are supplied only to subjects who are eligible to receive it and at the specified dose(s) and time(s)

3. the subjects are provided with the necessary instructions on proper handling of the product(s)

4. the receipt, use, return and disposal of the product(s) at the site are controlled and documented as prescribed

5. the investigator receives the current Investigator's Brochure and all supplies needed to conduct the study as per the protocol

6. the investigator follows the protocol

7. the investigator maintains the essential documents

8. all parties involved are adequately informed about various aspects of the study and follow the GCP guidelines and the prescribed SOPs

9. verifying that each party is performing the specified function in accordance with the protocol and / or in accordance with the agreement between the sponsor and the party concerned

10. verifying that none of the parties delegate any assigned function to unauthorised individuals

(d) The monitor should promptly inform the sponsor and the ethics committee in case any unwarranted deviation from the protocol or any transgression of the principles embodied in GCP is noted.

(e) The monitor should follow a pre-determined written set of SOPs. A written record should be kept of the monitor's visits, phone calls and correspondence with the investigators and any other involved parties.

(f) The monitor should assess the institution(s) prior to the study to ensure that the premises and facilities are adequate and that an adequate number of subjects is likely to be available during the study.

(g) The monitor should observe and report the subject recruitment rate to the sponsor.

(h) The monitor should visit the investigator before, during and after the study to make assessments of the protocol compliance and data handling in accordance with the predetermined SOPs.

(i) The monitor should ensure that all staff assisting the investigator in the study have been adequately informed about and will comply with the protocol, SOPs and other details of the study.

(j) The monitor should assist the investigator in reporting the data and results of the study to the sponsor, e.g. by providing guidance on correct procedures for CRF completion and by providing data verification.

(k) The monitor shall be responsible for ensuring that all CRFs are correctly filled out in accordance with original observations, are legible, complete, and dated. The monitor should specifically verify that

1. the data required by the protocol are reported accurately on the CRFs and are consistent with the source documents

2. any dose and / or therapy modifications are well documented for each of the study subjects

3. adverse events, concomitant medications and inter-current illnesses are promptly reported on the CRFs in accordance with the protocol and the SOPs

4. visits that the subjects fail to make, tests that are not conducted and examinations that are not performed are clearly reported as such on the CRFs

5. all withdrawals and drop-outs of enrolled subjects from the study are reported and explained on the CRFs

(l) Any deviations, errors or omissions should be promptly clarified with the investigator, corrected and explained on the CRF. Monitor should also take appropriate actions designed to prevent recurrence of detected deviations. Monitor should ensure that investigator certifies the accuracy of CRF by signing it at the places provided for the purpose. All procedures for ensuring accuracy of CRFs must be maintained throughout the course of the study.

(m) The monitor should submit a written report to the sponsor after each site visit and after all telephone calls, letters and other correspondence with the investigator. Monitor's report should include the date, name of site, names of the monitor and the individuals contacted, a summary of what the monitor reviewed, findings, deviations & deficiencies observed, and any actions taken / proposed to secure compliance. The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

(n) The monitor should confirm that the prescribed procedures for storage, handling, dispensing and return of investigational product are being followed and their compliance is being documented in a form as in the SOPs.

3.3. Investigator

3.3.1. Qualifications

The investigator should be qualified by education, training and experience to assume responsibility for the proper conduct of the study and should have qualifications prescribed by the Medical Council of India (MCI). The investigator should provide a copy of the curriculum vitae and / or other relevant documents requested by the sponsor, the ethics committee, the CRO or the regulatory authorities. He / she should clearly understand the time and other resource demands the study is likely to make and ensure they can be made available throughout the duration of the study. The investigator should also ensure that other studies do not divert essential subjects or facilities away from the study at hand.

The investigator should be thoroughly familiar with the safety, efficacy and appropriate use of the investigational

product as described in the protocol, investigator's brochure and other information sources provided by the sponsor from time to time.

The investigator should be aware of and comply with GCPs, SOPs and the applicable regulatory requirements.

3.3.2. Medical care of the study subjects

A qualified Medical Practitioner (or a Dentist, when appropriate) who is an Investigator or a Co-Investigator for the study should be responsible for all study related medical decisions. Investigator has to ensure that adequate medical care is provided to a subject for any adverse events including clinically significant laboratory values related to the study. Investigator should inform the subject when medical care is needed for inter-current illness(es) of which the investigator becomes aware. Investigator should also inform the subject's other attending physician(s) about the subject's participation in the study if the subject has another attending physician(s) and if the subject agrees to such other physician(s). Subsequent to the completion of the study or dropping out of the subject(s) the investigator should ensure that medical care and relevant follow-up procedures are maintained as needed by the medical condition of the subject and the study and the interventions made.

Although a subject is not obliged to give reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the subject's rights.

3.3.3. Monitoring and Auditing of Records

The investigator / institution shall allow monitoring and auditing of the records, procedures and facilities, by the sponsor, the ethics committee, CRO or their authorised representative(s) or by the appropriate regulatory authority. The investigator should maintain a list of appropriately qualified person(s) to whom the investigator has delegated study-related duties.

Investigator should ensure that all persons involved in the study are adequately informed about the protocol, SOPs, the investigational product(s) and their study related duties and functions.

3.3.4. Communication with Ethics Committee

Before initiating a study the investigator / institution must ensure that the proposed study has been reviewed and accepted in writing by the relevant ethics committee(s) for the protocol, written informed consent form, subject recruitment procedures (e.g. advertisements) and any written / verbal information to be provided to the subjects.

The investigator should promptly report to the ethics committee, the monitor and the sponsor:

1. deviations from or changes of, the protocol to eliminate immediate hazards to the subjects
2. changes that increase the risk to subject(s) and / or affecting significantly the conduct of the study
3. all adverse drug reactions and adverse events that are serious and / or unexpected
4. new information that may adversely affect safety of the subjects or the conduct of the study

4. new information that may adversely affect safety of the subjects or the conduct of the study

5. for reported deaths the investigator should supply any additional information e.g. autopsy reports and terminal medical reports.

3.3.5. Compliance with the protocol

The investigator / institution must agree and sign the protocol and / or another legally acceptable document with the sponsor, mentioning the agreement with the protocol, and confirm in writing that he / she has read and understood the protocol, GCPs and SOPs and will work as stipulated in them.

The investigator may implement a deviation from, or change of protocol to eliminate an immediate hazard(s) to study subjects without prior ethics committee approval / favourable opinion. The implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment(s) should be submitted by the investigator to the ethics committee (for review and approval / favourable opinion), to the sponsor (for agreement) and if required to the regulatory authority(ies).

The investigator or person designated by him/her should document and explain any deviation from the approved protocol. The Investigator should follow the study randomisation procedure, if any, and should ensure that the randomisation code is broken only in accordance with the Protocol. If the study is blinded, the Investigator should promptly document and explain to the Sponsor any premature un-blinding e.g. accidental un-blinding, un-blinding due to serious adverse event) of the Investigational Product(s).

3.3.6. Investigational Product(s)

Investigator has the primary responsibility for investigational product(s) accountability at the study site(s). Investigator should maintain records of the product's delivery to the study site, the inventory at the site, the use by each subject, and the return to the sponsor or the alternative disposal of the unused product(s). These records should include dates, quantities, batch / serial numbers, expiry dates if applicable, and the unique code number assigned to the investigational product packs and study subjects. Investigator should maintain records that describe that the subjects were provided the dosage specified by the protocol and reconcile all investigational products received from the sponsor. Investigator should ensure that the product(s) are stored under specified

conditions and are used only in accordance with the approved protocol.

The investigator should assign some or all of his / her duties for investigational product's accountability at the study site(s) to his subordinate who is under the supervision of the investigator / institution. The investigator or subordinate should explain the correct use of the product(s) to each subject and should check at intervals appropriate for the study that each subject is following the instructions properly. The person who carries them out should document such periodic checks.

3.3.7. Selection and recruitment of study subjects:

The investigator is responsible for ensuring the unbiased selection of an adequate number of suitable subjects according to the protocol. It may be necessary to secure the co-operation of other physicians in order to obtain a

according to the protocol. It may be necessary to secure the co-operation of other physicians in order to obtain a sufficient number of subjects. In order to assess the probability of an adequate recruitment rate for subjects for the study it may be useful to determine prospectively or review retrospectively the availability of the subjects. Investigator should check whether the subject(s) so identified could be included in the study according to the protocol. The investigator should keep a confidential list of names of all Study Subjects allocated to each study. This list facilitates the investigator / institution to reveal identity of the subject(s) in case of need and also serve as a proof of Subject's existence. The investigator / institution shall also maintain a Subjects' screening log to document identification of Subjects who enter pre-study screening. A Subject's enrolment log shall also be maintained to document chronological enrolment of Subjects in a particular Study.

The Investigator is responsible for giving adequate information to subjects about the trial in accordance with the GCP. The nature of the investigational product and the stage of development and the complexity of the study should be considered in determining the nature and extent of the information that should be provided.

Obligations of investigators regarding informed consent: The investigator has the duty to -

1. Communicate to prospective subjects all the information necessary for informed consent. There should not be any restriction on subject's right to ask any questions related to the study as any restriction on this undermines the validity of informed consent.

2. Exclude the possibility of unjustified deception, undue influence and intimidation. Deception of the subject is not permissible However, sometimes information can be withheld till the completion of study, if such information would jeopardize the validity of research.

3. Seek consent only after the prospective subject is adequately informed. Investigator should not give any unjustifiable subject's decision to participate in the study.

4. As a general rule obtain from each prospective subject a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related to the trial, and in case of incompetence to do so, a legal guardian or other duly authorised representative.

5. Renew the informed consent of each subject, if there are material changes in the conditions or procedures of the research or new information becomes available during the ongoing trial.

6. Not use intimidation in any form which invalidates informed consent. The investigator must assure prospective subjects that their decision to participate or not will not affect the patient-clinician relationship or any other benefits to which they are entitled.

As part of the information provided to the Subject, the Investigator should supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about contact persons who can assist in an emergency situation.

3.3.8. Records/Reports

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to the CRF should be dated, signed and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections.

Sponsor should provide guidelines to investigators and / or the investigator's designated representatives on making such corrections and should have written procedures to assure that changes in CRFs are documented and endorsed by the Investigator. The Investigator should retain records of the changes and corrections.

Progress Reports

The investigator should submit the written summaries of the study status at the periodicity specified in the protocol to the person(s) / organisation(s) to whom the investigator is reporting. All reportings made by the investigator should identify the subjects by unique code numbers assigned to the study subjects rather than by the subjects' name(s), personal identification number(s) and / or addresses.

Termination and final report:

In case the investigator and sponsor agree to prematurely terminate or suspend the study for any reason, the investigator / institution should promptly inform the study Subjects, the Ethics Committee as well as the Regulatory Authorities. The investigators should also ensure appropriate therapy and follow-up for the subjects.

However, if the investigator or the sponsor or the ethics committee decide to terminate or suspend the study without prior agreement of all parties concerned then the party initiating the suspension / termination should promptly inform all the concerned parties about such suspension / termination and suspension along with a detailed written explanation for such termination / suspension.

The Investigator should maintain documents as specified in the essential documents' list and take measures to prevent accidental or premature destruction.

The study can be closed only when the Investigator (or the Monitor or CRO – if this responsibility has been delegated to them) has reviewed both Investigator / Institution and Sponsor files and confirm that all necessary documents are in the appropriate files.

The completion of the study should be informed by the investigator to the institution, the sponsor and the ethics committee. The investigator should sign and forward the data (CRFs, results and interpretations, analyses and reports, of the study from his / her centre to the sponsor and the ethics committee. Collaborative investigators and those responsible for the analyses (including statistical analyses) and the interpretation of the results must also sign the relevant portions of the study report. Investigator should submit his signed and dated final report to the institution, the ethics committee and the sponsor verifying the responsibility for the validity of data.

In case of a multi-centre study – the signature of the co-ordinating investigator may suffice if agreed in the protocol.

In case the investigator is the sponsor then he / she assumes the responsibilities of both the functionaries. 367

The investigator should familiarise himself / herself with the various other responsibilities assigned to him/her under the protocol and ensure that they are carried out as expected.

RECORD KEEPING AND DATA HANDLING

The basic concept of record-keeping and handling of data is to record, store, transfer, and where necessary convert efficiently and accurately the information collected on the trial subject(s) into data that can be used to compile the Study Report.

4.1. Documentation

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of data quality and study performance for the purpose of audit. Following the SOPs facilitates documentation.

Documentation SOPs should include details of checklists and forms giving details of actions taken, dates and the individuals responsible etc.

4.2. Corrections

All corrections in the CRFs or any other study related documents should be made in a way that does not obscure the original entry. The correct data should be inserted with the reason for the correction if such a reason is not obvious. The corrections should carry the date and initials of the Investigator or the authorised person.

4.3. Electronic Data Processing

For electronic data processing only authorised person should be allowed to enter or modify the data in the computer and there should be a recorded trail of the changes and deletions made. A security system should be set-up to prevent unauthorised access to the data. If data is altered during processing the alteration must be documented and the system should be validated. The systems should be designed to permit data changes in such a way that the data changes are documented and there is no deletion of data once it has been entered. A list of authorised persons who can make changes in the computer system should be maintained. Adequate backup of the data should be maintained.

4.4. Validation of Electronic Data Processing Systems

If trial data are entered directly into the computer there must always be an adequate safeguard to ensure validation including a signed and dated printout and backup records. Computerised systems – hardware as well as software - should be validated and a detailed description of their use be produced and kept up-to-date.

4.5. Language

All written documents, information and other material used in the Study should be in a language that is clearly understood by all concerned (i.e. the Subjects, paramedical staff, Monitors etc.)

4.6. Responsibilities of the Investigator

Investigator should ensure that the observations and findings are recorded correctly and completely in the CRFs and signed by the responsible person(s) designated in the Protocol.

Laboratory values with normal reference ranges should always be recorded on a CRF or enclosed with the CRF. Values outside the clinically accepted reference range or values that differ importantly from previous values must be evaluated and commented upon by the Investigator. Data other than that requested by the Protocol may appear on the CRF clearly marked as the additional findings and their significance described by the investigator. Units of measurement must always be stated and transformation of units must always be indicated and documented.

In the medical records of the patient(s) it should be clearly indicated that the individual is participating in a clinical trial.

4.8. Responsibilities of the Sponsor and the Monitor

The sponsor must ensure that electronic data processing system conforms to the certain documented requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation). The Sponsor must maintain SOPs for using these systems. The Monitor should take adequate measures to ensure that no data is overlooked. If the computer system automatically assigns any missing values – the fact should be clearly documented.

Sponsor should safeguard the blinding, if any, particularly during data entry and processing. The Sponsor should use an explicit Subject identification code that allows identification of all the data reported for each Subject. Ownership of the data and any transfer of the ownership of data should be documented and intimated to the concerned party(ies).

QUALITY ASSURANCE

The Sponsor is responsible for the implementation of a system of Quality Assurance in order to ensure that the Study is performed and the data is generated, recorded and reported in compliance with the Protocol, GCP and other applicable requirements. Documented Standard Operating Procedures are a prerequisite for quality assurance.

All observations and findings should be verifiable, for the credibility of the data and to assure that the conclusions presented are correctly derived from the Raw Data. Verification processes must therefore be specified and justified.

Statistically controlled sampling may be an acceptable method of data verification in each Study. Quality control must be applied to each stage of data handling to ensure that all data are reliable and have processed correctly.

Sponsor's audits should be conducted by persons independent of those responsible for the Study. Investigational sites, facilities, all data and documentation should be available for inspection and audit by the Sponsor's auditor as well as by the Regulatory Authority(ies).

STATISTICS

6.1. Role of a Biostatistician

Involvement of a appropriately qualified and experienced statistician is necessary in the planning stage as well as throughout the Study. The Bio-statistician's should make a statistical model to help the Sponsor, CRO and / or the Investigator in writing the Protocol. The number of Subjects to be included in the study is determined in relation to the statistical model on which the Protocol is based.

6.2. Study Design:

The scientific integrity of a Clinical Study and the credibility of its report depends on the design of the Study. In comparative studies the Protocol should describe:

1. an "a priori" rationale for the target difference between treatments that the Study is being designed to detect, and the power to detect that difference, taking into account clinical and scientific information and professional judgment on the clinical significance of statistical differences.

2. measures taken to avoid bias, particularly methods of Randomisation.

6.2.1. Randomisation and blinding:

The key idea of a clinical trial is to compare groups of patients who differ only with respect to their treatment. If the groups differ in some other way then the comparison of treatment gets biased. Randomisation, as one of the fundamental principles of experimental design, it deals with the possible bias at the treatment allocation. It ensures that the allocation of treatment to human subjects is independent of their characteristics. Another important benefit of Randomisation is that statistical methods of analysis are based on what we expect to happen in random samples from populations with specified characteristics. The Protocol must state the method used for Randomisation.

The Study should use the maximum degree of blindness that is possible. Study subjects, investigator or any other party concerned with the study may observe and respond by knowledge of which treatment was given. To avoid such bias it is often desired that the patient or any other person involved with the study does not know which treatment was given. Where a sealed code for each individual treatment has been assigned in a blinded randomized study it should be kept both at the site of the investigation and with the sponsor.

The Protocol must state the conditions under which the code is allowed to be broken and by whom. The system of breaking the code should be such that it allows access to only one Subject's treatment at a time. The coding system for the Investigational Product(s) should include a mechanism that permits rapid identification of the products in case of a medical emergency, but does not permit undetectable breaks of the blinding.

6.3. Statistical Analysis

The type(s) of Statistical Analyses to be used must be clearly identified and should form basis of the statistical model for the Study. Any subsequent deviation(s) should be described and justified in the Final Report. The need and extent of an interim analysis must be specified in the Protocol. The results of the statistical analyses should be presented in a manner that is likely to facilitate the interpretation of their clinical importance, e.g. by estimates of the magnitude of the treatment effect / difference and confidence intervals rather than sole reliance on significance testing.

Missing, unused and spurious data should be accounted for during the statistical analyses. All such omissions must be documented to enable review.

SPECIAL CONCERNS

7.1 Clinical Trials of Vaccines

7.1.1 Phases of Vaccine Trials

The guidelines to conduct the clinical trial on investigational vaccines are similar to those governing a clinical trial. The phase of these trials differ from drug trials as given below:

Phase I: This refers to the first introduction of a vaccine into a human population for determination of its safety and biological effects including immunogenicity. This phase includes study of dose and route of administration and should involve **low risk subjects**. For example, immunogenicity to hepatitis vaccine should not be determined in high-risk subjects.

Phase II: This refers to the initial trials examining effectiveness (immunogenicity) in a limited number of volunteers. Vaccines can be prophylactic and therapeutic in nature. While prophylactic vaccines are given to normal subjects,

therapeutic or curative vaccines may be given to patients suffering from particular disease.

Phase III: This focuses on assessments of safety and effectiveness in the prevention of disease, involving controlled study on a larger number of volunteers (in thousands) in multi-centres.

7.1.2. Guidelines

- The sponsor and investigator should be aware of the approval process(es) involved in conducting clinical trials of vaccines. They should familiarize themselves with the guidelines provided by Drug Controller General (India), Department of Biotechnology (DBT) and Ministry of Environment and Genetic Engineering Approval Committee (GEAC) in the case of vaccines produced by recombinant DNA technology. See Appendix III.
- Some vaccines that contain active or live-attenuated microorganisms can possibly possess a small risk of producing that particular infection. The subjects to be vaccinated should be informed of the same.
- The subjects in control groups or when subjected to ineffective vaccines run a risk of contracting the disease.
- The risks associated with vaccines produced by recombinant DNA techniques are not completely known. However, for all the recombinant vaccines/products the guidelines issued by the Department of Biotechnology should be strictly followed.
- Trials should be conducted by investigator with the requisite experience and having necessary infrastructure for the laboratory evaluation of seroconversion.
- Protocols for such trials should include appropriate criteria for selection of subjects, plan of frequency of administration of the test vaccine in comparison with the reference vaccine. It should accompany detailed validation of testing method to detect the antibody titter levels.
- It should specify methodology to be adopted for prevention of centrifuged serum for the purpose of testing.
- The investigator should be provided with Quality Control data of the experimental batch of the vaccine made for the purpose of clinical trials.
- The sponsor should provide the Independent Ethics Committee approval of the nodal body (ies) to carry out clinical trials with the vaccine.
- The generic version of new vaccines already introduced in the other markets after step up clinical trials including extensive Phase III trials should be compared with the reference vaccine with regard to seroconversion in a comparative manner in a significant sample size.
- Post Marketing Surveillance (PMS) should be required following seroconversion studies. PMS data should be generated in a significant sample size sensitive to detect side effects and address other safety issues.
- Protocols for test of new vaccine should contain a section giving details of steps of manufacture, in-process quality control measures, storage conditions, stability data and a flow chart of various steps taken into consideration for manufacture of vaccine. It should also contain detailed method of quality control procedure with the relevant references.

7.2. Clinical Trials of Contraceptives

- All procedures for clinical trials are applicable. Subjects should be clearly informed about the alternative available.
- In women where implant has been used as a contraceptive for trial, a proper follow up for removal of the implant should be done, whether the trial is over or the subject has withdrawn from the trial.
- Children borne due to failure of contraceptives under study should be followed up for any abnormalities if the woman does not opt for medical termination of pregnancy.

7.3 Clinical trials with surgical procedures/ medical devices

Of late, biomedical technology has made considerable progress in the conceptualisation and designing of bio-equipments. Several medical devices and critical care equipments have been developed and many more are in various stages of development. However, only through good manufacturing practices (GMP) can the end products reach the stage of utilization by society. Most of these products are only evaluated by Central Excise testing for taxation purposes, which discourages entrepreneurs to venture in this area with quality products especially when they do not come under the strict purview of the existing regulatory bodies like ISI, BSI and Drug Controller General. This is evidenced by the very low number of patents or propriety medical equipments manufactured and produced in the country. As the capacity of the country in this area is improving day by day the need for a regulatory mechanism/ authority is increasingly obvious. The concept of regulations governing investigations involving biomedical devices is therefore relatively new in India. At present, except for needles and syringes these are not covered by the Drugs and Cosmetics Act, 1940. The Chief Executive of the Society of Biomedical Technology (SBMT) set up under the Defence Research Development Organisation (DRDO) has drafted a proposal for the setting up of a regulatory, tentatively named as the Indian Medical Devices Regulatory Authority (IMDRA). Until the guidelines are formulated and implemented by this regulatory Authority clinical trials with biomedical devices should be approved on case to case basis by committees constituted for the specific purpose.

7.3.1. Definitions:

Medical devices: A medical device is defined as an inert diagnostic of therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body unlike the medicated devices which contain pharmacologically active substances which are treated as drugs. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intra-ocular lenses, orthopaedic pins and other orthopaedic accessories.

Depending upon risks involved the devices could be classified as follows:

a. Non critical devices: An investigational device that does not present significant risk to the patients e.g. Thermometer, B.P. apparatus.

b. Critical devices: An investigational device that presents a potential risk to the health, safety, welfare of the subject- for example, pacemakers, implants, internal catheters.

All the general principles of clinical trials described for clinical trials should also be considered for trials of medical devices. As for the drugs, safety evaluation and pre-market efficacy of devices for 1-3 years with data on adverse reactions should be obtained before pre-market certification. The duration of the trial and extent of use may be decided in case to case basis by the appropriate authorities. However, the following important factors that are unique to medical devices should be taken into consideration while evaluating the related research projects.

7.3.2. Guidelines

- Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.
- A clinical trial of medical devices is different from drug trials, as former can not be done in healthy volunteers. Hence phase I of drug trial is not necessary for trial on devices.
- Medical devices used within the body may have greater risk potential than those used on or outside the body, for example, orthopaedic pins Vs crutches.
- Medical device not used regularly have less risk potential than those used regularly, for example, contact lens Vs intraocular lenses.
- Safety procedures to introduce a medical device in the patient should also be followed as the procedure itself may cause harm to the patient.
- Informed consent procedures should be followed as in drug trials. The patient information sheet should contain information on following procedures to be adopted if the patient decides to withdraw from the trial.

7.4. Clinical trials for Diagnostic Agents - Use of Radio-active Materials and X- Rays

In human beings, for investigation and treatment, different radiations- X-rays, gamma rays and beta rays, radio opaque contrast agents and radioactive materials are used. The relative risks and benefits of research proposal utilizing radioactive materials or X-rays should be evaluated. Radiation limits for the use of such materials and X-Rays should be in accordance with the limits set forth by the regulatory authority (BARC) for such materials. (BARC-Bhabha Atomic Research Centre, Mumbai).

7.4.1. Guidelines

§ Informed consent should be obtained before any diagnostic procedures.

§ Information to be gained should be gathered using methods that do not expose subjects to more radiation than exposed normally.

§ Research should be performed on patients undergoing the procedures for diagnostic or therapeutic purposes.

§ Safety measures should be taken to protect research subjects and others who may be exposed to radiation.

§ The protocol should make adequate provisions for detecting pregnancies to avoid risks of exposure to the embryo.

§ Information to subject about possible genetic damage to offspring should be given.

§ Non-radioactive diagnostic agents are considered as drugs and the same guidelines should be followed when using them.

§ Ultrasound to be submitted wherever possible.

7.5 Clinical trials of Herbal Remedies and Medicinal Plants

For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the DCG (I) for allopathic drugs should be followed. This does not pertain to guidelines issued for clinical evaluation of Ayurveda, Siddha or Unani drugs by experts in those systems of medicine which may be used later in their own hospitals and clinics. All the general principles of clinical trials described earlier pertain also to herbal remedies. However, when clinical trials of herbal drugs used in recognized Indian systems of Medicine and Homoeopathy are to be undertaken in Allopathic Hospitals, associations of physicians from the concerned system as co-investigators/ collaborators/ members of the expert group is desirable for designing and evaluating the Study.

7.5.1. Categories of Herbal Products

The herbal products can belong to any of the three categories given below:

a. A lot is known about the use of a plant or its extract in the ancient Ayurveda, Siddha or Unani literature or the plant may actually be regularly used by physicians of the traditional systems of medicine for a number of years. The substance is being clinically evaluated for same indication for which it is being used or as has been described in the texts.

b. When an extract of a plant or a compound isolated from the plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it has to be treated as a new substance or new chemical entity (NCE) and the same type of acute, subacute and chronic toxicity data will have to be generated as required by the regulatory authority before it is cleared for clinical evaluation.

c. An extract or a compound isolated from a plant which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug, and therefore, should undergo all regulatory requirements before being evaluated clinically.

7.5.2. Guidelines

- It is important that plants and herbal remedies currently in use or mentioned in literature of recognized Traditional System of Medicine is prepared strictly in the same way as described in the literature while incorporating GMP norms for standardization. It may not be necessary to undertake phase I studies. However, it needs to be emphasized that since the substance to be tested is already in used in Indian Systems of Medicine or has been described in their texts, the need for testing its toxicity in animals has been considerably reduced. Neither would any toxicity study be needed for phase II trial unless there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months. It should be necessary to undertake 4-6 weeks toxicity study in 2 species of animals in the circumstances pointed out in the preceding sentence or when a larger multicentric phase III trial is subsequently planned based on results of phase II study.

- Clinical trials with herbal preparations should be carried out only after these have been standardized and markers identified to ensure that the substances being evaluated are always the same. The recommendations made earlier regarding informed consent, subject, inducements for participation, information to be provided to the subject, withdrawal from study and research involving children or persons with diminished autonomy, all apply to trials on plant drugs also. These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes. However, it is essential that such clinical trials be carried out only when a competent Ayurvedic, Siddha or Unani physician is a co-investigator in such a clinical trial. It would neither ethically acceptable nor morally justifiable, if an allopathic physician, based on references in ancient literature of above-mentioned traditional systems of Medicine, carries out clinical evaluation of the plant without any concept or training in these systems of medicine. Hence, it is necessary to associate a specialist from these systems and the clinical evaluation should be carried out jointly.

- When a Folklore medicine / Ethno-medicine is ready for commercialisation after it has been scientifically found to be effective, then the legitimate rights/ share of the Tribe or Community from whom the knowledge was gathered should be taken care of appropriately while applying for the Intellectual Property Rights and / Patents for the product.

APPENDICES

Appendix I:

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. A appropriate precaution must be observed in the conduct of research which may affect the environment, and the welfare of

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix II:

SCHEDULE Y

Requirements and guidelines on clinical trials for import and manufacture of new drug

1. ***Clinical Trials***

1. *Nature of trials*: The clinical trials required to be carried out in the country before a new drug is approved for

marketing depend on the status of the drug in other countries. If the drug is already approved/marketed, phase III trials as required under item 7 of Appendix I (to Sch. Y) usually are required. If the drug is not approved/ marketed, trials are generally allowed to be initiated at one phase earlier to the phase of trials in other countries.

For new drug substances discovered in other countries phase I trials are not usually allowed to be initiated in India unless phase I data as required under Item 5 of the said Appendix from other countries are available. However, such trials may be permitted even in the absence of phase I data from other countries if the drug is of special relevance to the health problem of India.

For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase I as required from Item 5 of the said Appendix, through phase III as required under Item 7 of the said Appendix, permission to carry out these trials is generally given in stages, considering the data emerging from earlier phase.

2. *Permission for trials:* Permission to initiate clinical trials with a new drug may be obtained by applying in Form 12 for a test license (TL) to import or manufacture the drug under the Rules. Data appropriate for the various phases of clinical trials to be carried out should accompany the application as per format given in Appendix I (Items I-4). In addition, the protocol for proposed trials, case report forms to be used, and the names of investigators and institutions should also be submitted for approval. The investigators selected should possess appropriate qualifications and experience and should have such investigational facilities as are germane to the proposed trials protocol.

Permission to carry out clinical trials with a new drug is issued along with a test license in Form 11.

It is desirable that protocols for clinical trials be reviewed and approved by the institution's ethical committee. Since such committees at present do not exist in all institutions, the approval granted to a protocol by the ethical committee of one institution will be applicable to the use of that protocol in other institutions, which do not have an ethical committee. In case none of the trial centres/institutions has an ethical committee the acceptance of the protocol by the investigator and its approval by the Drugs Controller (India) or any officer as authorized by him to do so will be adequate to initiate the trials.

For new drugs having potential for use in children, permission for clinical trials in the paediatric age group is normally given after phase III trials as required under item 7 of the said Appendix, in adults are completed. However, if the drug is of value primarily in a disease of children, early trials in the paediatric age group may be allowed.

3. *Responsibilities of Sponsor/Investigator:* Sponsors are required to submit to the Licensing Authority as given under Rule 21 an annual status report on each clinical trial, namely, ongoing, completed, or terminated. In case a trial is terminated, reason for this should be stated. Any unusual, unexpected, or serious adverse drug reaction (ADR) detected during a trial should be promptly communicated by the sponsor to the Licensing Authority under Rule 21 and the other investigators.

   In all trials an informed, written consent is required to be obtained from each volunteer/patient in the prescribed

   form (See Appendix V), which must be signed, by the patient/volunteer and the chief investigator.

2. ***Chemical and Pharmaceutical Information***

Most of the data under this heading (See Appendix I to Sch. Y, Item 2) are required with the application for marketing permission. When the application is for clinical trials only, information covered in item 2.1 to 2.3 of Appendix I will usually suffice.

3. ***Animal Toxicology***

1. *Acute toxicity:* Acute toxicity studies (See Appendix I – Sch. Y - Item 4.2) should be carried out in at least two species, usually mice and rats using the same route as intended for humans. In addition, at least two more route should be used to ensure systemic absorption of the drug, this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parenteral administration and up to 7 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD 50s should be reported preferably with 95 percent confidence limits, if LD 50s cannot be determined, reasons for this should be stated.

2. *Long-term toxicity:* Long-term toxicity studies (see Appendix I – Sch. Y, Item 1.3) should be carried out in at least two mammalian species, of which one should be a non-rodent. The duration of study will depend on whether the application is for marketing permission or for clinical trial, and in the later case, on the phases of trials (see Appendix III). If a species is known to metabolize the drug in the same way as humans, it should be preferred.

   In long-term toxicity studies the drug should be administered 7 days a week by the route intended for clinical use in humans. The number of animals required for these studies, i.e. the minimum number on which data should be available, is shown in Appendix IV to Sch. Y.

   A control group of animals, given the vehicle alone, should always be included, and three other groups should be given graded doses of the drug; the highest dose should produce observable toxicity, the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it, eg: 2.5x to make allowance for the sensitivity of the species; the intermediate dose should cause some symptoms, but not gross toxicity or death, and may be placed logarithmically between the other two doses.

   The variables to be monitored and recorded in long-term toxicity studies include behavioral, physiological, biochemical and microscopic observations.

3. *Reproduction studies:* Reproduction studies (see Appendix I – Sch. Y, item 4.4) need to be carried out only if the new drug is proposed to be studied or used in women of childbearing age. Two species should generally be used, one of them being non-rodent if possible.

(a)Fertility studies: The drug should be administered to both males and females, beginning a sufficient number of days before mating. In females the medication should be continued after mating and the pregnant one should be treated throughout pregnancy. The highest dose used should not affect general health or growth of the animals. The route of administration should be the same as for therapeutic use in humans. The control and the treated group should be of similar size and large enough to give at least 20 pregnant animals in the control group of rodents and at least 8 pregnant animals in the control group of non-rodents. Observations should include total examination of the litters from both the groups, including spontaneous abortions, if any.

(b)Teratogenicity studies: The drugs should be administered throughout the period of organogenesis, using three dose levels. One of the doses should cause minimum maternal toxicity and one should be the proposed dose for clinical use in humans or multiple of it. The route of administration should be the same as for human therapeutic use. The control and the treated groups should consist of at least 20 pregnant females in case of non-rodents, on each dose used. Observations should include the number of implantation sites, resorptions if any; and the number of fetuses with their sexes, weights and malformations if any.

(c) Perinatal studies: The drug should be administered throughout the last third of pregnancy and then through lactation and weaning. The control of each treated group should have at least 12 pregnant females and the dose which causes low foetal loss should be continued throughout lactation weaning. Animals should be sacrificed and observations should include macroscopic autopsy and where necessary, histopathology.

4.Local toxicity: These studies (see Appendix I, Sch. Y, Item 4.5) are required when the new drug Is proposed to be used typically in humans. The drug should be applied to an appropriate site to determine local effects in a suitable species such as guinea pigs or rabbits, if the drug is absorbed from the site of applications, appropriate systemic toxicity studies will be required.

5.*Mutagenicity and Carcinogenicity :* These studies (see Appendix I, Sch. Y Item 4,6) are required to be carried out if the drug or its metabolite is related to a known carcinogen or when the nature and action of the drug is such as to suggest a carcinogenic/mutagenic potential. For carcinogenicity studies, at least two species should be used. These species should not have high incidence of spontaneous tumors and should preferably be known to metabolize the drug in the same manner as humans. At least three does levels should be used; the highest does should be sub-lethal but cause observable toxicity; the lowest does should be comparable to the intended human therapeutic does or a multiple of it, eg: 2.5x; to make allowance for the sensitivity of the species; the intermediate does to be placed logarithmically between the other two doses. A control group should always be included. The drug should be administered 7 days a week or a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Observations should include macroscopic changes observed at autopsy and detailed histopathology.

4. Animal Pharmacology

Specific pharmacological actions (see Appendix I to Sch. Y, Item 3.2) are those with therapeutic-potential for humans. These should be described according to the animal models and species used. Wherever possible, dose-response relationships and ED 50s should be given. Special studies to elucidate mode of action may also be described.

General pharmacological action (see Appendix I to Sch. Y, Item 3.3) are effects on other organs and systems, especially cardiovascular, respiratory and central nervous systems.

Pharmacokinetic data help relate drug effect to plasma concentration and should be given to the extent available.

5. Human/Clinical Pharmacology trials (Phase I)

The objective of phase I of trials (see Appendix I, Sch. Y, Item 5) is to determine the maximum tolerated dose in humans; pharmacodynamic effects, adverse reactions, if any, with their nature and intensity; and pharmacokinetic behaviors or the drug as far as possible. These studies are carried out in healthy adult males, using clinical, physiological and biochemical observations. At least 2 subjects should be used on each dose.

Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centers.

6. Exploratory trials (Phase II)

In phase II trial (see Appendix I to Sch. Y, Item 6) a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centers and carried out by clinicians specialized on the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

7. Confirmatory trials (Phase III)

The purpose of these trials (see Appendix I to Sch. Y, Item 7) is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made.

If the drug is a new drug substance discovered in India and not marketed in any other country, phase III data should be obtained on at least 500 patients distributed over 10-15 centers. In addition, data on adverse drug reactions observed during clinical use of the drug as recommended and to provide a report on its efficacy and adverse drug reactions in the treated patients. The selection of clinicians for such monitoring and supply of drug to them will need approval of the licensing authority under Rule-21 of Drugs & Cosmetics Rules.

8. Special Studies

(A) These include studies on solid oral dosage forms, such as, bioavailability and dissolution studies. These are required to

(A) These include studies on solid oral dosage forms, such as, bioavailability and dissolution studies. These are required to be submitted on the formulations manufactured in the country. (See Appendix I, Items 8.1 and 8.2)

(B) These include studies to explore additional aspects of the drug, eg: use in elderly patients or patients with renal failure, secondary or ancillary effects, interactions, etc. (See Appendix I to Sch. Y, Item 8.1 and 8.2).

9. Submission of Reports (Appendix II to Schedule Y)

The reports of completed clinical trials shall be submitted by the applicant duly signed by the investigator within a stipulated period of time. The applicant should do so even if he is no longer interested to market the drug in the country unless there are sufficient reasons for not doing so.

10. Regulatory status in other counties

It is important to state if any restrictions have been placed on the use of the drug in any other country, eg: dosage limits, exclusion of certain age groups, warnings about adverse drug reaction, etc. (See Appendix I, Sch. Y, Item 9.2)

Likewise, if the drug has been withdrawn from any country especially by a regulatory directive such information should e furnished along with reasons and their relevance, if any, to India (See Appendix I, Item 9.1(d)).

11. Marketing Information

The product monograph should comprise the full prescribing information necessary to enable a physician to use the drug properly. It should include description, actions, indications, dosage precaution, drug interactions, warnings and adverse reactions.

The drafts of label and carton texts should comply with provisions of Rules 96 and 97 of the said rules.

Appendix I to Schedule Y

Data required to be submitted with application for permission to market a new drug

1. Introduction

A brief description of the drug and the therapeutic class to which it belongs.

2. Chemical and pharmaceutical information

1. Chemical name; code name or number, if any; non-proprietary or generic name, if any; physio-chemical proportion.
2. Dosage form and its composition.
3. Specifications of active and inactive ingredients.
4. Tests for identification of the active ingredient and method of its assay.
5. Outline of the method of manufacture of the active ingredient.
6. Stability data.

3. Animal pharmacology

1. Summary.
2. Specific pharmacological actions.
3. General pharmacological actions.
4. Pharmacokinetics, absorptions, distribution, metabolism, excretion.

4. Animal toxicology (See Appendix III and IV to Sch. Y)

1. Summary
2. Acute toxicity
3. Long term toxicity
4. Reproduction studies
5. Local toxicity
6. Mutagenicity and carcinogenicity

5. Human/clinical pharmacology (Phase I)

1. Summary.
2. Specific pharmacological actions.
3. General pharmacological actions.
4. Pharmacokinetics, absorptions, distribution, metabolism, excretion.

6. Exploratory clinical trials (Phase II)

1. Summary

2. Investigator wise reports.

7. Confirmatory clinical trials (Phase III)

1. Summary
2. Investigator wise reports.

8. Special studies

1. Summary
2. Bioavailability and dissolution studies.
3. Investigator wise reports.

9. Regulatory status in other countries

1. Countries where

    (a) Marketed

    (b) Approved

    (c) Under trial, with phase

    (d) Withdrawn, if any, with reasons

2. Restrictions on use, if any, in countries where marketed/approved.
3. Free sale certificate from country of origin.

10. Marketing information

1. proposed product monograph
2. Drafts of labels and cartons
3. Sample of pure drug substance, with testing protocol

Notes I: All items may not be applicable to all drugs, for explanation, see text of Schedule Y.

II: For requirements of data to be submitted with application for clinical trials see text of Schedule Y, Section I and also Appendices II and III to Sch. Y.

APPENDIX I to Schedule YI

Format for submission of Clinical Trial Reports

….Title of the trial

….Name of the investigator and institution

….Objectives of the trial

….Design of study: open, single-blind or double-blind, non-comparative or comparative; parallel group or crossover.

….Number of patients, with criteria for selection and exclusion; whether written informed consent, was obtained.

….Treatments given: drugs and dosage forms: regimens; method of allocations of patients to the treatments; method of verifying compliance, if any.

….Observations made before, during and at the end of the treatment, for efficacy and safety , with methods used.

….Results: exclusions and dropouts, if any, with reasons; description of patients with initial comparability of groups where appropriate; clinical and laboratory observations on efficacy and safety; adverse drug reactions.

….Discussions of results: relevance to objectives, correlation with other reports data, if any; guidance for further study, if necessary.

….Summary and conclusion.

APPENDIX III to Schedule Y

Animal toxicity requirements for clinical trials and marketing of a new drug

Route of administration	Duration of Human administration	Phase	Long term toxicity requirements
Single dose or several doses in one Day		I-III, MP	2sp; 2 wk
Oral or Parenteral or Transdermal	Up to 2 wk	I, II	2sp; Up to 4 wk
		III, MP	2sp: Up to 3 mo
	Up to 3 wk	I, II	2sp; 4 wk
		III	2sp; 3 mo
		MP	2sp; up to 6 mo
	Over 3 mo	I,II	2sp; 3 mo
		III, MP	2sp; 6 mo
Inhalation (general anaesthetics)		I:III, MP	4sp; 5d (3h/d)
Aerosol	Repeated or Chronic use		I:II 1-2 sp; 3h/exp.

		III	1-2 sp; Up to 6wk, (2 exp/d)
Dermal	Short term or Long term application	MP I,II	1-2 sp; 24wk (2 exp/d) 1 sp; single 24th exp; then 2 wk observation
			1 sp; **
Ocular or Otic or Nasal	Single or Multiple application	III:MP I:II	Irrigation test; graded doses
		III	1 sp; 3 wk; daily applications as in clinical use.
			1 sp; **
Vaginal or Rectal	Single or Multiple application	MP I, II, III, MP	1 sp; **

** Number and/or duration of application commensurate with duration of use

Abbreviations: sp- species; wk- week; d- day; h- hour; mo- month; MP – Marketing Permission; exp- exposure I, II, III – Phases of clinical trial (see Appendix I, item No. 5-8).

Note : (1) Animal toxicity data available from other countries are acceptable and do not need to be repeated/duplicated in India. (2) Requirements for fixed dose combinations are given in Appendix VI.

APPENDIX IV to Schedule Y

Number of animals for long term toxicity studies

2-6 Weeks Group	Rodents (rats)		Non-Rodents (dogs)		7-26 Weeks Rodents (rats)		Non-Rodents (dogs)	
	M	F	M	F	M	F	M	F
Control	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Low dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Interme-diate dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
High dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6

APPENDIX V to Schedule Y

Patient consent form for participation in a Phase I Clinical Trial

This clinical trial involves the study of a new …….….. agent in volunteers/patients suffering from ……..

The drug which will be administered to volunteers/patients has been found to be safe in animal toxicity tests and other experimental data. The volunteers/patients will be required to undergo, if necessary, all routine examinations including taking of X-ray, ECG, EEG etc. at intervals. The volunteers/patients may be asked to collect stool and urine, and there may be need to draw blood or any other body fluid on several occasions to test the effects of concentrations of the drugs. The volunteers/patients are free to withdraw from the trial at any stage.

Authorisation

I have read/been briefed on the above project summary and I voluntarily agree to participate in the project. I understand that participation in this study may or may not benefit me. Its general purpose, potential benefits, possible hazards, and inconveniences have been explained to my satisfaction. I hereby give my consent for this treatment.

Signature or thumb impression

Name of the volunteer/patient

Date: Signature of Chief Investigator

Patient consent form for participation in Phase II and Phase III Clinical Trial

I …… exercising my free power of choice, hereby give my consent to be included as a subject in the clinical trial of a new drug, namely ……. for the treatment of …….. . I understand that I may be treated with this drug for the diseases. I am suffering from …….. . I have been informed to my satisfaction, by the attending physician the purpose of the clinical trial and the nature of drug treatment and follow up including the laboratory investigation to monitor and safeguard my body function.

I am also aware of my right to opt out of the trial at any time during the course of the trial without having to give the reasons for doing so.

Signature of the patient

Date:

Signature of the attending physician

APPENDIX VI to Schedule Y

Data requirements of Fixed Dose Combinations

Fixed Dose combinations (FDC) fall into four groups and their data requirements accordingly

(a) The first group of FDC includes those in which one or more of the active ingredients is a new drug. Such FDC are treated in the same way as any other new drug , both the clinical trials and for marketing permission (see Rule 122-E, Item (a)).

(b) The second group of FDC includes those in which active ingredients already approved/marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature (see Rule 122-E, item (c)). For permission to carry out clinical trials with such FDC, a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredient as well as their combinations in the proposed ratio. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated. (See Appendix I, Item 9).

For marketing permission, the reports of clinical trials carried out with the FDC in India should be submitted. The nature of trials depending on the claims to be made and the data already available.

(c) The third group of FDC includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim.

(d) The fourth group of FDC includes those whose individual active ingredients have been widely used in particular indication for years, there concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage form and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

No additional animals or human data are generally required for these FDC, and marketing permission may be granted if the FDC has an acceptable rationale.

APPENDIX III

FORMAT FOR SUBMISSION OF PRECLINICAL AND CLINICAL DATA*

FOR r-DNA BASED VACCINES, DIAGNOSTICS AND OTHER BIOLOGICALS

(Reproduced from Guidelines for Generating Preclinical and Clinical Data for r-DNA based vaccines, diagnostics and other biologicals issued by Department of Biotechnology, Ministry of Science and Technology, Govt. of India)

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*For details to generate these data, please consult the document entitled " Guidelines for generating preclinical and clinical data for r-DNA based vaccines, diagnostics and other biologicals".

A : SPECIFICATION AND CHARACTERIZATION INFORMATION ON r-DNA VACCINES AND BIOLOGICAL PRODUCTS

1. **Description in details of the method of r-DNA products:**

   (a) host cells,

   (b) gene construct,

   (c) vector construction including a description of the source and function of the component parts of the vectors,

   (d) source and diagram of the plasmid(s) used,

   (e) all intermediate cloning procedures, and

   (f) transfection methods.

Description of the method of sequence verification (such as restriction enzyme mapping, PCR etc.).

3. **Description on Identity-Physical, Chemical, Immunological and Biological wherever applicable**

   (a) Description on recombinant DNA products :

      (1) Primary structure (Amino acid sequences)

      (2) Secondary structure (disulfide linkages etc.)

      (3) Post-translation modification (glycosylation etc.)

   (b) Monoclonal antibodies (if applicable) :

      - identity by rigorous immunochemical and physicochemical characterization.

4. **Potency.**

   (a) Production of specific antigen in transfected cell line,

   (b) Immune response in mice,

   (c) Hypersensitivity (Guinea pig maximization test), and

   (d) Permissible limits of potency.

5. **General Safety Test.**

6. **Data on sterility tests as per Indian Pharmacopia guidelines.**

7. **Data on purity of recombinant product.**

   (a) Limits of purity,

   (b) Characterization of minor impurities like RNA, protein and genomic DNA,

   (c) Permissible limits of moisture, if lyophilized, and

   (d) Pyrogenicity

8. **Description of constituent materials like preservatives etc.**

9. **Data on stability of finished formulation as per IP (Indian pharmacopia) guidelines.**

B : DATA ON PRECLINICAL TESTING

1. Biological activity/ pharmacodynamics *in vitro* and in appropriate animal models.
2. Safety Pharmacology (Functional indices of toxicity).
3. Toxicology and pharmacokinetics (Absorption, Distribution, Metabolism, Excretion- ADME)
4. Immunogenicity/Immunotoxicity
5. Reproductive and developmental toxicity
6. Genotoxicity studies
7. Carcinogenicity studies

C: RECOMBINANT IMMUNODIAGNOSTIC REAGENTS

1. Specification and characterization of r-DNA diagnostic products (Please provide information as per column1-9 under Section A of this format).
2. The data on the sensitivity / specificity / predictive positive value/ predictive negative value / overall diagnostic accuracy of recombinant product in diagnostic assay.
3. Data on (1) "in-house" validation and (2) independent validation.
4. Data using indigenous / internationally available panel of sera / clinical materials.

D: CLINICAL TRIALS

1. **Phase I : Human/Clinical Pharmacology Immunogenic Potency**

    (a) Details on level of specific antibodies including its kinetics in healthy subjects.

    (b) Details on cytokine profiles in healthy subjects.

    (c) Details on T-cell responses in healthy subjects.

    (d) Data on auto-antibodies and immune complexes in healthy subjects.

    (e) Details on haematological and clinical chemistry.

2. **Phase II: Exploratory Clinical Trials- Preventive/Therapeutic Efficacy (Data to be generated in subjects residing in endemic/ non-endemic areas)**

    (a) Protective / therapeutic potentials of r-DNA vaccines.

    (b) Details of the haematological data.

(c) Details on the clinical chemistry.

(d) Data on experiments on minimum protective / therapeutic dose vis-à-vis immune response (both T&B cells).

3. **Phase III: Confirmatory Trials**

(a) Preventive / therapeutic effects.

(b) Immunological / clinical chemistry parameters in some subjects belonging to different ethnic and socio-economic groups.

APPENDIX IV

INVESTIGATOR'S BROCHURE (IB)

Introduction

The Investigator's Brochure is a compilation of the clinical and non-clinical data on the Investigational Product(s) that are relevant to a study of the product(s). It provides the investigator(s) and others involved in the study with the information on the rationale to facilitate compliance with the key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB also provides background material to support the clinical management of the study subjects. The information contained in the IB should be in a concise, simple, objective, balanced, and non-promotional form to enable an understanding unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data. The IB should be revised whenever necessary in compliance with the sponsor's written procedures, the stage of development and the generation of relevant new information. However, any relevant new information that is considered important should be communicated to the Investigator(s), Ethics Committee and the Regulatory Authorities immediately, even before it can be methodically included in the IB.

Contents of the Investigator's Brochure

The IB should include Sponsor's name, the reference number allocated to the study, the identity of each investigational product (ie. research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor). The IB should bear an edition number and date. Besides, wherever applicable it also bears a reference to the number and date of the edition it supersedes.

The Sponsor may wish to include a statement instructing the readers to treat the IB as a confidential document for the sole purpose of the Study for which it has been prepared.

The IB should contain the following sections, each with literature references where appropriate:

1 Table of Contents

2 Introduction: This section includes information relevant to the stage of clinical development including the significant physical properties , chemical properties, pharmaceutical, pharmacological (pharmacological class, advantages over other substances in that class and rationale for performing the proposed study), toxicological, pharmacokinetic, metabolic, and clinical information (anticipated prophylactic/ therapeutic or diagnostic indication(s)) of all active ingredients. The introductory statement should necessarily provide the general approach to be followed in evaluating the Investigational Product.

3 Physical, Chemical, and Pharmaceutical Properties and Formulation parameters: A description should be provided of the Investigational Product substance(s), including the chemical and / or structural formula(e), and a brief summary of the relevant physical, chemical and pharmaceutical properties. Any structural similarities to other known compounds should be mentioned. Information should also be provided on the excipients.

Appropriate storage and dosage handling instructions should also be given.

4 Non-clinical Studies: Information provided should include data relating to non-clinical pharmacology, pharmacokinetics, metabolism profile in animals and toxicology. The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and the Investigational Product metabolism studies should be provided in summary form, stating the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic effects besides the possible unfavourable effects in humans.

The information provided may include the following, as appropriate, if known/available:

· Species used

· Number and sex of animals in each group

· Unit dose (mg/kg)

· Dose interval

· Route of administration

· Duration of dosing

· Information on systemic distribution

· Duration of post-exposure follow-up

· Results, including the following aspects:

- Nature and frequency of pharmacological or toxic effects

- Severity or intensity of pharmacological or toxic effects

- Time to onset of effects

- Time to onset of effects

- Reversibility of effects

- Duration of effects

- Dose response

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and non-toxic dose findings in the same animal species should be compared (i.e. The therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Non-clinical Pharmacological (Pharmacodymanics)

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (eg. special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose

- Repeated dose

- Carcinogenicity

- Special studies (eg. irritancy and sensitisation)

-Reproductive toxicity

- Genotoxicity (mutagenicity)

5 Effects in Humans:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on

pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Brief summaries of other clinical studies conducted on the same product should be provided if available.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational

product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (eg. gender, age, and impaired organ function).

Interactions (eg. Product-product interactions and effects of food).

Other pharmacokinetic data (eg. results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

Information should be provided about the Investigational Product(s)' (including their metabolites, where appropriate) safety pharmacodynamics, efficacy and dose response(s) that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of the information should be discussed. In cases where a number of clinical studies have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Regulatory & Post-marketing Experiences

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (eg. formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

6 Summary of Data and Guidance for the Investigator

7 Bibliography

This section should provide an overall discussion of the non-clinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. Available published reports on related products should be discussed.

The information given in this section should provide the investigator with a clear understanding of the possible risks and adverse reactions.

Guidance should also be provided on the recognition and treatment of possible overdose and adverse drug reactions.

APPENDIX V

ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

Essential Documents are those documents which individually and collectively allow the evaluation of the conduct of a study and the quality of the data generated. These documents demonstrate the compliance (or otherwise) of the Investigator, Sponsor and Monitor with the Good Clinical Practice and with other applicable regulatory requirements.

Essential Documents are needed for Sponsor's independent audit function and inspection by the Regulatory Authority.

The various Essential Documents needed for different stages of the study are classified under three groups:

1. before the clinical phase of the study commences,
2. during the clinical conduct of the study, and
3. after completion or termination of the study.

The documents may be combined but their individual elements should be readily identifiable.

Master files containing all documents pertaining to the study should be created at the beginning of the study, at the Investigator /

Institution site, Sponsor's office, Ethics committee's office and the CRO's office.

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Legend :

I - Investigator / Institute, S - Sponsor, C - CRO,

E - IEC, · - Yes, ° - Not applicable

	Title of the document	Purpose	Located in files of			
			I	**S**	**C**	**E**
Before the Clinical Phase of the Trial Commences						
During this planning stage the following documents should be generated and should be on file before the trial formally starts.						
1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	·	·	·	·
2	Signed protocol and amendments, if any, and sample case report form(CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	·	·	·	·
3	Information given to trial subject - informed consent form (including all applicable translations)	To document the informed consent	·	·	·	·
4	- Any other written information	To document that subjects will be given appropriate information (content and wording) to support their ability to give fully informed consent	·	·	·	·
5	- Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	·	·	·	·
6	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	·	·	·	·
7	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	·	·	·	·

	Title of the document	Purpose	Located in files of I	S	C	E
8	Dated, documented approval / favourable opinion of independent ethics committee (IEC) of the following: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - Subject compensation (if any) - any other documents given approval / favourable opinion	To document that the trial has been subject to IEC review and given approval / favourable opinion. To identify the version number and date of the document(s)	·	·	·	·
9	Independent ethics committee composition	To document that the IEC is constituted in agreement with GCP	·	·	·	·
10	Regulatory authority(ies) authorisation / approval / notification of protocol (where required)	To document appropriate authorisation / approval / notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	·	·	·	·
11	Curriculum vitae and/or other relevant documents evidencing qualifications of Investigator(s) and Co-Investigator / Sub-Investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	·	·	·	·
12	Normal value(s) / range(s) for medical / laboratory / technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	·	·	·	°
	Title of the document	Purpose	**Located in files of I**	**S**	**C**	**E**
13	Sample of label(s) attached to investigational product	To document compliance with applicable labelling regulations and	·	·	·	°

	container(s)	appropriateness of instructions provided to the subjects				
14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	·	·	·	°
15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	·	·	·	°
16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational product(s) to be used in the trial	°	·	·	°
	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subject's treatment	·	·	·	°
17	Master randomisation list	To document method for randomisation of trial population	°	·	·	°
18	Pre-trial monitoring report	To document that the site is suitable for trial (may be combined with Trial initiation monitoring report)	°	·	·	°
19	Trial initiation monitoring report	To document that the trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with Pre-trial monitoring report)	·	·	·	°

	Title of the document	Purpose	**Located in files of**			
			I	**S**	**C**	**E**
During the Clinical Conduct of the Trial						
In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available						
20	Investigator's brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	·	·	·	·
21	Any revision to: - protocol amendment(s) and CRF - informed consent form - any other written information provided to	To document revisions of these trial related documents that take effect during trial	·	·	·	·

	subjects - advertisement for subject recruitment(if used)					
22	Dated, documented approval / favourable opinion of Independent ethics committee (IEC) of the following: - protocol amendment(s) - revision(s) of: - informed consent form - any other written information provided to subject - advertisement for subject recruitment(if used) - any other documents given approval / favourable opinion - continuing review of trial (where required)	To document that the trial has been subject to IEC review and given approval / favourable opinion. To identify the version number and date of the document(s).	·	·	·	·

	Title of the document	Purpose	**Located in files of**			
			I	**S**	**C**	**E**
23	Regulatory authority(ies) authorisations / approvals / notifications where required for: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	·	·	·	·
24	Curriculum vitae for new investigator(s) and / or sub- investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	·	·	·	·

25	Updates to normal value(s)/ range(s) for medical/laboratory/ technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial	·	·	·	°
26	Medical/laboratory/technical procedures/tests - certification or - accreditation or - established quality control and / or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period	·	·	·	°
27	Documentation of investigational product(s) and trial-related material shipment	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	·	·	·	°
28	Certificate(s) of analysis for new batches of investigational products	To document identity, purity, and strength of investigational product(s) to be used in the trial	°	·	·	°
29	Monitoring visit reports	To document site visits by, and findings of, the monitor	°	·	·	°
30	Relevant communications other than site visits - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	·	°	·	°

	Title of the document	Purpose	**Located in files of**			
			I	**S**	**C**	**E**
31	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission	· (Original)	· (Copy)	· (Copy)	°
32	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trials, to medical treatment, and history of subject	· (Original)	· (Copy)	· (Copy)	°

33	Signed, dated and completed case report forms (CRF)	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	· (Copy)	· (Copy)	· (Copy)	°
34	Documentation of CRF corrections	To document all changes / additions or corrections made to CRF after initial data were recorded	· (Original)	· (Copy)	· (Copy)	°
35	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports	·	·	·	·
36	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IEC(s) of unexpected serious adverse drug reactions and of other safety information	·	·	·	·

	Title of the document	Purpose	**Located in files of**			
			I	**S**	**C**	**E**
37	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information	·	·	·	·
38	Interim or annual reports to IEC and authority(ies)	Interim or annual reports provided to IEC and to authority(ies)	·	·	·	·
39	Subject screening log	To document identification of subjects who entered pre-trial screening	·	· (Where required)	· (Where required)	°

40	Subject identification code list	To document that investigator / Institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ Institution to reveal identity of any subject	·	·	·	°
41	Subject enrolment log	To document chronological enrolment of subjects by trial number	·	·	·	°
42	Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol	·	·	·	°
43	Signature sheet	To document signatures and initials of all persons authorised to make entries and / or corrections on CRFs	·	·	·	°
44	Record of retained body fluids/ tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	·	·	·	°

	Title of the document	Purpose	Located in files of I	S	C	E
After Completion or Termination of the Trial						
After completion or termination of the trial, all of the documents identified should be in the file together with the following						
45	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, return by the subjects, and returned to sponsors	·	·	·	°
46	Documentation of investigational product destruction	To document destruction of unused investigational products by sponsor or at site	· (if destroyed at site)	·	·	°
47	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	·	·	·	°
48	Audit certificate (if available)	To document that audit was performed	°	·	·	°

(if available)

49	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	°	·	·	°
50	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred	°	·	·	°

	Title of the document	Purpose	**Located in files of**			
			I	**S**	**C**	**E**
51	Final report by investigator to IEC where required, and where applicable, to the regulatory authority(ies)	To document completion of the trial	·	·	·	·
52	Clinical study report	To document results and interpretation of trial	·	·	·	·

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ANNEXURE R/11

Recommendations of the SEC meeting to examine COVID-19 related proposal under accelerated approval process made in its 130th meeting held on 09.12.2020 at CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
Biological Division			
1.	BIO/CT/20/000182 mRNA vaccine (Phase I/II)	M/s Gennova Biopharmaceuticals Limited, Pune	The firm presented their proposal for grant of permission to conduct Phase I/II clinical trial along with animal toxicity study data before the committee. After detailed deliberation, the committee recommended for grant of permission to conduct Phase I/II clinical trial subject to the condition that the interim results of Phase I study shall be submitted to the committee before proceeding to the next phase.
2.	BIO/MA/20/000102 ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (EUA)	M/s Serum Institute of India Pvt. Ltd., Pune	The firm presented their proposal for grant of Emergency Use Authorization (EUA) of ChAdOx1 nCoV-19 vaccine (COVISHIELD) along with the interim safety data from Phase II/III clinical trial carried out in the country and the interim safety and efficacy results of Phase II/III and Phase III clinical trials carried out in UK, other countries & India before the committee. The committee noted that as per the condition of the permission to conduct phase II/III clinical trial in the country, the clinical data generated in the trial shall be considered along with the data from the OXFORD clinical trial outcome. Further, the firm stated that the proposal for grant of emergency use authorization is currently under evaluation with MHRA. It is also noted that the Phase II/III clinical trial is still ongoing in the country. Further, the firm has submitted the safety data till 14.11.2020 only. After detailed deliberation, the committee recommended that the firm should submit the following data/information for further review: 1. Updated safety data of the Phase II/III clinical trial in the country. 2. Immunogenicity data from the clinical trial in UK and India. 3. The outcome of the assessment of UK-MHRA for grant of EUA. Dr. Sushant Meshram did not participate in the discussion.

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
3.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA)	M/s Bharat Biotech International Limited, Hyderabad	The firm presented their proposal for grant of Emergency Use Authorization (EUA) of Whole Virion, Inactivated Corona Virus Vaccine (BBV152) along with the interim safety and immunogenicity data of Phase I and II clinical trial carried out in the country before the committee. After detailed deliberation, the committee recommended that the firm should present the safety and efficacy data from the ongoing Phase III clinical trial in the country for further consideration.
4.	BIO/IMP/20/000110 COVID-19 mRNA Vaccine BNT162b2	M/s Pfizer Ltd., Mumbai	The firm has requested more time for making presentation before the committee.

Recommendations of the SEC meeting to examine COVID-19 related proposal under accelerated approval process made in its 133rd meeting held on 30.12.2020 at CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
Vaccine Division			
1.	BIO/MA/20/000102 ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (EUA)	M/s Serum Institute of India Pvt. Ltd. (SIIPL), Pune	In light of the earlier recommendations the firm presented safety immunogenicity & efficacy data of phase II/III clinical trials of AstraZeneca vaccine carried out in UK & Brazil & South Africa along with the safety & immunogenicity data from the ongoing Phase II/III clinical trial of COVISHIELD vaccine manufactured by SIIPL in the country. The firm also presented the draft factsheet & prescribing information of the vaccine. The firm also mentioned that AstraZeneca had received Emergency Use Authorization for the vaccine in UK subject to various conditions & restrictions. The committee discussed the safety, efficacy & immunogenicity data, draft factsheet & prescribing information as provided by the firm & decided that clarification/justification on various aspects are still needed. After detailed deliberation, the committee recommended that the firm should submit complete details of the conditions & restrictions under which AstraZeneca was granted Emergency Use Authorization in UK and also present the revised factsheet & prescribing information in Indian context as required by the committee for further consideration. Also the firm was informed during the meeting regarding other requirements including clarification/justification on factsheet & prescribing information.
2.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA)	M/s Bharat Biotech International limited, Hyderabad	In light of the earlier recommendations of the committee, the firm presented updated recruitment status & safety data including SAE data of the ongoing Phase III clinical trial in the country. After detailed deliberation, the committee recommended that firm should update & present Immunogenicity, Safety & Efficacy data for further consideration.
3.	BIO/IMP/20/000110 COVID-19 mRNA Vaccine BNT162b2	M/s Pfizer Ltd., Mumbai	The firm did not turn up for the presentation

Recommendations of the SEC meeting to examine COVID-19 related proposals under accelerated approval process made in its 134th meeting held on 01.01.2021 CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
Biological Division			
1.	BIO/MA/20/000102 ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (COVISHIELD)	M/s Serum Institute of India Pvt Ltd.	In light of the recommendations of the committee in its earlier meeting dated 30.12.2020, the firm presented the details of the conditions & restrictions under which AstraZeneca was granted Emergency Use Authorization in UK and the revised factsheet & prescribing information in Indian context as required by the committee for further consideration. Further, the firm also presented the proposed Summary of Product Characteristics (SmPC) and risk management plan including Pharmacovigilance plan. The committee deliberated on various critical areas for consideration including safety, immunogenicity, efficacy data, indication, age group, dosing schedule, precautions, storage, warnings, adverse effects of special interest, risk benefit evaluation, proposed factsheet, PI, SmPC, Risk management plan etc. The committee reviewed the proposal of restricted emergency use along with above details in its meetings dated 09.12.2020, 30.12.2020 and 01.01.2021 as well as reviewed continuously the data as and when received. The MHRA approval dated 30.12.2020 along with its conditions/restrictions was also reviewed by the committee. The committee noted that the safety & immunogenicity data presented by the firm from the Indian study is comparable with that of the overseas clinical trial data. Considering the serious nature of the COVID-19 pandemic, emergency situation, there is an urgent need of vaccine in the country. After detailed deliberation, the committee recommended for grant of permission for restricted emergency use of the vaccine subject to various regulatory provisions including following: **1.** The vaccine is indicated for active immunization to prevent COVID-19 disease in individuals of ≥ 18 years of age. **2.** The vaccine should be administered intramuscularly in two doses of 0.5 ml each (containing $5x10^{10}$ vp per dose) with interval of 4 to 6 weeks. **3.** The vaccine should be supplied along with factsheet & separate leaflet for the guidance of the healthcare provider. **4.** The firm should submit the updated PI,

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
			SmPC & factsheet incorporating the changes as discussed during the meeting. **5.** The firm should ensure that factsheet for the vaccine recipient/his attendant is provided prior to administration of the vaccine. **6.** The firm should disseminate the instructions & educational material including factsheet, PI, SmPC, storage instructions etc. in their website. **7.** The firm should submit safety, efficacy & immunogenicity data from the ongoing clinical trials nationally and internationally for review at the earliest. **8.** The firm should submit safety data including the data on AEFI and AESI with due analysis every 15 days for the first two months & monthly thereafter till the completion of the ongoing clinical trial in the country. Thereafter, the firm should submit the safety data as per the provisions and standard procedures. **9.** The firm should submit India specific Risk management plan. Dr. Sushant H Meshram didn't participate in this deliberation.
2.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA)	M/s Bharat Biotech International limited, Hyderabad	In light of the earlier recommendations of the committee dated 30.12.2020, the firm presented safety & immunogenicity data, GMT, GMFR including SAE data from the Phase I & Phase II clinical trial along with the data from the ongoing Phase III clinical trial in the country. The committee noted that this vaccine is Inactivated Whole Virion, Corona Virus Vaccine having potential to target mutated corona virus strains. The data generated so far demonstrates a strong immune response (both antibody as well as T cell) and in-vitro viral neutralization. The ongoing clinical trial is a large trial on 25800 Indian subjects in which already 22000 subjects have been enrolled including subjects with comorbid conditions as well which has demonstrated safety till date. However, efficacy is yet to be demonstrated. After detailed deliberation, the committee recommended that the firm should try to expedite the recruitment and may perform interim efficacy analysis for further consideration of restricted emergency use approval.
3.	BIO/IMP/20/000110 COVID-19 mRNA	M/s Pfizer Ltd., Mumbai	The firm did not turn up for the deliberation.

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
	Vaccine BNT162b2		

Recommendations of the SEC meeting to examine COVID-19 related proposals under accelerated approval process made in its 135th meeting held on 02.01.2021 CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendations
Biological Division			
1.	BIO/CT/20/000194 Novel Corona Virus 2019-nCoV vaccine	M/s Cadila Healthcare Limited, Ahmedabad	The firm presented interim safety and immunogenicity data of ongoing Phase I/II clinical trial of Novel Corona Virus 2019-nCoV vaccine along with proposed phase III clinical trial protocol before the committee. After detailed deliberation, the committee recommended for grant of permission for conduct of proposed phase III clinical trial protocol subject to the condition that the vaccine efficacy should be assessed on the data generated after day 84 from the first dose.
2.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (EUA)	M/s Bharat Biotech International limited, Hyderabad	In light of the recommendations of the committee dated 01.01.2021, the firm further presented the updated data, justification and requested for consideration of their proposal in the wake of incidence of new mutated corona virus infection. As already noted by the committee, this vaccine is Inactivated Whole Virion, Corona Virus Vaccine having potential to target mutated corona virus strains. The data generated so far demonstrates a strong immune response (both antibody as well as T cell) and in-vitro viral neutralization. The ongoing clinical trial is a large trial on 25800 Indian subjects in which already 22500 subjects have been enrolled including subjects with comorbid conditions as well which has demonstrated safety till date. Moreover, firm has presented the safety and efficacy data from Non-human primate challenge study where the vaccine has been found to be safe and effective. In view of above, after detailed deliberation, the committee recommended for grant of permission for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, to have more options for vaccinations, especially in case of infection by mutant strains. Further, the firm shall continue the on-going Phase III clinical trial and submit data emerging from the trial as and when available.

Recommendations of the SEC meeting to examine COVID-19 related proposal under accelerated approval process made in its 146th meeting held on 10.03.2021 at CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendation
Biological Division			
1.	BIO/MA/20/000103 Whole Virion, Inactivated Corona Virus Vaccine (BBV152) (Phase III interim report)	M/s Bharat Biotech, International Limited, Hyderabad	In continuation to the SEC meeting dated 08.03.2021, firm presented updated interim safety and efficacy data of its phase III clinical trial of Whole Virion, Inactivated Corona Virus Vaccine (BBV152) in the country. The committee noted that the firm has carried out interim analysis after 43 cases of symptomatic RT-PCR positive COVID-19 have been reported out of which 36 were in the placebo arm and 7 in the vaccine arm. After detailed deliberation, the committee recommended for omission of the condition of the use of the vaccine in clinical trial mode. However, the vaccine should be continued to be used under restricted use in emergency situation condition. Further, the ongoing phase III clinical trial should be continued as per the approved protocol. The firm should update the prescribing information and factsheet accordingly (under restricted use in emergency situation condition). All other conditions of the marketing authorisation shall continue to remain effective.

Recommendations of the SEC meeting to examine COVID-19 related proposal under accelerated approval process made in its 161st meeting held on 22.06.2021 at CDSCO, HQ New Delhi:

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendation
New Drug Division			
1.	12-01/21-DC (pt-166) IV Artesunate IV Infliximab Tab Imatinib	ICMR - National AIDS Research Institutes	The applicant presented their proposal before the committee. After detailed deliberation, the committee recommended for approval of protocol subject to the conditions that 1. Artesunate arm shall not be recommended in view of non availability of data. 2. The definition for 'Moderate' to be elaborated to include the respiratory frequency 24-30 3. Standard of Care to be well defined and uniform across the sites. 4. RT-PCR, and not rapid antigen testing, shall be used for diagnosis of COVID -19.
2.	12-01/20-DC (pt-333) Anti-Corona Virus Therapies	St John Research Institute	In light of earlier recommendation dated 01.06.2021, the firm presented the revised clinical trial protocol for conduct of study in mild Covid patients. After detailed deliberation, the committee recommended for grant of permission to conduct the trial in mild COVID-19 patients with following conditions:-. 1. Standard of Care to be well defined and uniform across the sites. 2. RT-PCR, and not rapid antigen testing, shall be used for diagnosis of COVID -19
3.	ND/CT/20/000096 Carbohydrate derived Fulvic Acid	M/s Sphaerapharma	In the light of earlier recommendation of the SEC held on 17-12-2020 & 18-12-2020, the firm presented the proposal for Fulvic Acid , which is a family of many organic acids. The firm could not present any data on characterization of the organic acids, PK, PD, Safety efficacy data of the product. The product is not approved as drug even for clinical trial in any country.

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendation
			Therefore, the Committee did not recommend for approval of the proposed Clinical Trial.
4.	ND/CT-21/FF/21/26235 Aviptadil Solution for inhalation 67 mcg/ml	M/s Biosphere	The firm presented their proposal for approval of manufacture and marketing the drug "Aviptadil Inhalation" as Emergency use approval for moderate to severe Covid-19 treatment with waiver of CT & BE trial. After detailed deliberation, the committee recommended that the firm should present the detailed data on PK/PD, safety, efficacy of aviptadil by inhalation route to consider the matter further.
Biological Division			
5.	BIO/CT/21/000077 Adenoviral Vector COVID-19 Vaccine (BBV 154) (Intranasal)	M/s Bharat Biotech International Ltd., Hyderabad	The firm presented interim safety & immunogenicity data from Phase I clinical trial of Adenoviral Vector COVID-19 Vaccine (BBV 154) (Intranasal) along with the Phase II clinical trial protocol. After detailed deliberation, the committee recommended for grant of permission to conduct the Phase II clinical trial as per the proposed protocol.
6.	BIO/CT/20/000159 Whole-virion Inactivated SARS-CoV-2 Vaccine BBV152	M/s Bharat Biotech International Ltd., Hyderabad	In continuation to the recommendation of SEC meeting dated 23.04.2021, the firm presented updated interim safety & efficacy data of Phase III clinical trial of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152). The committee noted that the firm has submitted safety & efficacy data till two months after the second dose along with final efficacy analysis after accrual of 130 cases of symptomatic RT-PCR positive COVID-19 as required to meet the primary endpoint. Out of 130 cases, 106 were reported in the placebo arm and 24 in the vaccine arm giving vaccine efficacy of 77.8%. Further, the committee noted that, currently Phase III clinical trials are ongoing After detailed deliberation, the committee recommended that the vaccine should be continued to be used under restricted use in

Agenda No	File Name & Drug Name, Strength	Firm Name	Recommendation
			emergency situation . Further, the phase III clinical trial should be continued as per the approved protocol. The firm should update the prescribing information and factsheet accordingly and submit to CDSCO for approval. With regards to the use of the vaccine in pregnant women, the committee recommended that the firm should submit additional safety data.

Revised Guidelines for implementation of National COVID Vaccination Program

India's National COVID Vaccination Program is built on scientific and epidemiological evidence, WHO guidelines and global best practices. Anchored in systematic end-to-end planning, it is implemented through effective and efficient participation of States/UTs and the people at large.

Government of India's commitment to the vaccination program has been unwavering and proactive from the beginning, from strengthening Research and Development capacity, to encouraging and enabling manufacturing and vaccinating each and every adult Indian safely, as fast as possible.

For the COVID vaccination program, Government of India initiated early and proactive steps as far back as April 2020:

- "Task Force for Focused Research on Corona Vaccine" (constituted in April 2020), to encourage domestic R&D of Drugs, Diagnostics and Vaccines, headed by Principal Scientific Advisor to the Government of India.

- "National Expert Group on Vaccine Administration for COVID-19" (NEGVAC), (constituted in August 2020), to formulate a comprehensive action plan for vaccine administration, co-chaired by Member (Health) NITI Aayog and Union Health Secretary.

- "Empowered Group on Vaccine Administration for COVID-19" (constituted in January 2021), to facilitate optimal utilization of technology to make COVID vaccination all inclusive, transparent, simple and scalable, headed by CEO, National Health Authority.

India's COVID vaccination program incorporates recommendations of the foremost experts in the field of immunization, public health, disease control and information technology. Based on scientific and epidemiological evidence, the programme gives priority to strengthening the country's healthcare system by protecting the professionals, health and frontline workers, manning it, as well as protecting the most vulnerable population groups.

COVID vaccination in the country commenced with vaccination to all Health Care Workers. The program was expanded with time to include vaccination of Front Line Workers, citizens more than 60 years of age, citizens more than 45 years of age and eventually citizens more than 18 years of age.

Under the National COVID Vaccination Program, from 16th January to 30th April 2021, 100% of vaccine doses were procured by Government of India and provided free of cost to State Governments. State Governments were in turn to administer vaccination free of cost to defined priority groups. To increase the pace of vaccination, participation of private hospitals was also enlisted where individuals could also chose to get vaccinated at a prescribed rate.

In response to the suggestions of many State Governments to be permitted the flexibility to procure vaccine directly and administer them as per their own prioritization based on local requirements, Government of India revised the Guidelines. Under the revised Guidelines effective from 1st May, 2021, Government of India was procuring 50% of the vaccine produced and was continuing to provide them to States free of cost for administering to priority groups. The State Government and private hospitals were now also empowered to directly procure from the remaining 50% vaccine pool.

Many States have however now communicated that they are facing difficulties in managing the funding, procurement and logistics of vaccines, impacting the pace of the National COVID Vaccination Program. It has also been noted that smaller and remoter private hospitals are also facing constraints.

Keeping in view the aforesaid aspects, the experiences gained from 1st May 2021 and the repeated requests received from States, the Guidelines for National COVID Vaccination Program have been reviewed and revised.

The main elements of the Revised Guidelines are as follows -

- Government of India will procure 75% of the vaccines being produced by the manufacturers in the country. The vaccines procured will continue to be provided free of cost to States/UTs as has been the case from the commencement of the National Vaccination Programme. These doses will be administered by the States/UTs free of cost to all citizens as per priority through Government Vaccination Centres.

- In respect of the vaccine doses provided free of cost by Government of India to the States, vaccination will be prioritized as the following:
    - Health Care Workers
    - Front Line Workers
    - Citizens more than 45 years of age
    - Citizens whose second dose has become due
    - Citizens 18 years & above

- Within the population group of citizens more than 18 years of age, States/UTs may decide their own prioritization factoring in the vaccine supply schedule.

- Vaccine doses provided free of cost by Government of India will be allocated to States/UTs based on criteria such as population, disease burden and the progress of vaccination. Wastage of vaccine will affect the allocation negatively.

- Government of India will provide States/UTs advance information of vaccine doses to be supplied to them. States/UTs should similarly, further allocate doses well in advance to districts and vaccination centers. They should also put in the public domain the information about the above availability at district and vaccination center level, and widely disseminate it among the local population, maximizing the visibility and convenience of citizens.

- In order to incentivize production by vaccine manufacturers and encourage new vaccines, domestic vaccine manufacturers are given the option to also provide vaccines directly to private hospitals. This would be restricted to 25% of their monthly production. States/UTs would aggregate the demand of private hospitals keeping in view equitable distribution between large and small private hospitals and regional balance. Based on this aggregated demand, Government of India will facilitate supply of these vaccines to the private hospitals and their payment through the National Health Authority's electronic platform. This would enable the smaller and remoter private hospitals to obtain timely supply of vaccines, and further equitable access and regional balance.

- The price of vaccine doses for private hospitals would be declared by each vaccine manufacturer, and any subsequent changes would be notified in advance. The private hospitals may charge up to a maximum of Rupees 150 per dose as service charges. State Governments may monitor the price being so charged.

- All citizens irrespective of their income status are entitled to free vaccination. Those who have the ability to pay are encouraged to use private hospital's vaccination centres.

- To promote the spirit of “Lok Kalyan”, use of non-transferable Electronic Vouchers which can be redeemed at private vaccination centers, will be encouraged. This would enable people to financially support vaccination of Economically Weaker Sections at private vaccination centres.

- The CoWIN platform provides every citizen the facility of conveniently and safely pre-booking vaccination appointments. All government and private vaccination centers would also provide onsite registration facility, available both for individuals as well as groups of individuals, for which detailed procedure is to be finalized and published by States/UTs, in order to minimize any inconvenience to citizens.

- States may also optimally utilize the Common Service Centres and Call Centres to facilitate prior booking by citizens.

The above revised program provides States/UTs with additional central government support across funding, procurement and logistics. It also facilitates scientific prioritization, wider access, harnessing of private sector capacity and flexibility at the state and local level.

The revised guidelines will come into effect from 21st June 2021 and will be reviewed from time to time.

Standard Operating Procedures

Reporting AEFIs in Co-WIN - SAFE-VAC

All AEFIs (minor, severe and serious) after COVID-19 vaccination will be reported and recorded in Co-WIN - SAFE-VAC. Vaccinators and District Immunization Officers have access to Co-WIN and can report AEFIs in the application against the concerned beneficiary.

Vaccinator

1. Vaccinator will enter the information of an AEFI case of a beneficiary in vaccinator module. The vaccinator can enter the information of AEFIs of only those beneficiaries who have been vaccinated by him/her only.
2. Vaccinator will enter the information of AEFI case against the concerned beneficiary and will fill the AEFI form with relevant information about the case. The case will be submitted into the application and a confirmation message with AEFI ID of the case will appear on the screen.
3. If a vaccinator receives information of an AEFI case vaccinated by another vaccinator, he/she should inform the detail of the case to Medical Officer/DIO and enter it into the AEFI register also at planning unit.

District Immunization Officer (DIO)

1. District Immunization Officer may receive the information of AEFI cases from persons who don't have access to Co-WIN, like, medical officers, other vaccinators, private practitioners etc, through hard copy of CRF or telephone. The DIO will enter the information of such cases into Co-WIN.
2. The DIO will access list of beneficiaries in "Manage Beneficiaries" module of Co-WIN and will search the beneficiary for which AEFI needs to be reported. The information will be entered into the format and will be submitted.
3. The DIO can see list of all AEFIs (minor, severe, serious) reported in his/her district under "AEFI line-list" module. The DIO will assess each and every case reported in the list based on the case information, will assign them appropriate category (minor/severe/serious) and will confirm by clicking on "verify" checkbox against each case in the list. This activity needs to be done on daily basis and all new reported AEFI cases to be categorized within 24 hrs. The category will appear as 'minor' by default and DIO can change and reassign the category against each case before verifying.
4. DIO will raise Case Reporting Format (CRF) of all severe and serious cases by clicking on "Raise CRF" for detailed reporting and investigation.
5. All severe and serious cases need to be investigated as per the AEFI operational guidelines and Preliminary Case Investigation Form (PCIF), Final Case Investigation Form (FCIF) need to be submitted within the timelines as per operational guidelines.
6. The DIO will not wait for the timeline dates and submit the investigation details as soon as possible to facilitate timely causality assessment of the cases.

District review meetings (under the chairmanship of DM/CMO)

In all review meetings at district level (including district AEFI committee meetings), the following points will also be included for review and action:

1. Number of minor, severe and serious AEFI cases reported in the district
2. Status of categorization of reported AEFIs and generation of CRFs for cases categorized as severe or serious.
3. Status of investigation of cases and submission of CRF, PCIF and FCIF into Co-WIN – SAFE-VAC.

State review meetings (under the chairmanship of CS/ACS/PS/MD NHM/DG Health)

In all review meetings at state level, including State AEFI Committee meetings, the following points will also be included for review and action:

1. Status of categorization of reported AEFIs
2. Status of investigation of cases and submission of CRF, PCIF and FCIF into Co-WIN – SAFE-VAC.
3. The minutes and frequency of the meetings of district AEFI committee meetings and state AEFI Committee meetings and status of causality assessment of cases.

ANNEXURE R/14

Press Information Bureau
Government of India
Ministry of Health and Family Welfare

17-February-2017 19:22 IST

Maximum Possible Marks to Indian NRA in WHO Assessment

WHO has completed the assessment of the status of the Indian vaccine regulatory system against WHO NRA Global Benchmarking Tool (GBT) for benchmarking and measured the maturity of the system. The assessment has been carried out by a WHO team comprising lead experts in different areas from WHO Headquarters Geneva, WHO India Country Office, experts drawn from the regulators of USA, Italy, Germany, Netherlands, Indonesia, Thailand and Egypt. The assessment has been done in respect of nine different functionalities and Indian NRA has been declared 'functional' with a maturity level of 4 i.e. the highest level as per currently evolved definitions in respect of 5 functions, and maturity level 3 in respect of 4 functions. While, maturity level 4 indicates good results and sustained improvement trends, maturity level 3 reflects systematic process based approach, early stage of systematic improvements, data availability regarding conformance to objectives and existence of improvement trends.

India is one of the main players in the pharmaceutical industry worldwide. The pharmaceutical industry covers conventional as well as biological medicinal products including vaccines, medical devices, and traditional medicines. India, as a large vaccine producing country, is currently supplying several vaccines to the UN agencies (UNICEF, WHO and PAHO).

A fully functional NRA is a pre-requisite for WHO prequalification of vaccines. One of the requirements to become eligible and retain prequalification status is to have the National Regulatory Authority (NRA) assessed as functional against the WHO published NRA indicators. WHO Prequalification Programme, as such, facilitates access to vaccines that meet the unified standards of quality, safety and efficacy as well as programme needs. The vaccine manufacturers can only apply for WHO vaccine prequalification if the NRA meets the standards of the WHO NRA published indicators i.e. WHO Global benchmarking Tool on functional regulatory system for vaccines.

World Health Organisation (WHO) has, based on a robust benchmarking tool developed over years in consultation with various experts drawn from across the globe, carried out assessment of the National Regulatory Authority (NRA) of India comprising the Central Drugs Standard Control Organisation (CDSCO), State Drug Regulatory Authorities, Pharmaco-vigilance Programme of India (PvPI) and Adverse Events Following Immunization (AEFI) structures at the Central and States levels. The nine functions included in the tool are National Regulatory System; Registration and Marketing Authorization; Vigilance; Laboratory Access and Testing; Regulatory Inspection; Clinical Trial Oversight; NRA Lot Release; Licensing Premises; and Market Surveillance and Control. The Global Benchmarking Tool (GBT) so developed has 63 indicators and 288 sub-indicators, out of which 150 are critical with the following maturity level definitions:

The result reflects the growing maturity of the Indian NRA emanating from a concerted effort by the Government in consultation WHO to build capacity and capability of the National Regulatory Authority over last

several years.

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SK

ANNEXURE R/15

Z-16025/05/2012 Imm p/f
Government of India
Ministry of Health & Family Welfare
Immunization Division
****

Nirman Bhawan, New Delhi
Dated: 8th December, 2020

OFFICE MEMORANDUM

With reference to the Ministry's order no. Z-16025/05/2012-Imm dated 19 April 2017, the following have been nominated as additional members to the existing National AEFI Committee, with the approval of Secretary (HFW):

1. Dr. Debashish Choudhary, Director-Professor and Head, Department of Neurology, GB Pant Institute of PGMER, New Delhi
2. Dr. (Prof.) Neeraj Pandit, Consultant and Head, Department of Cardiology, Dr Ram Manohar Lohiya Hospital and PGIMER, New Delhi
3. Dr. Karan Madan, Associate Professor, Department of Pulmonary Medicine and Sleep Disorders, All India Institute of Medical Sciences, New Delhi
4. Dr. Anil Gurtoo, Director-Professor, Department of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
5. Dr. Anju Seth, Director-Professor, Department of Paediatrics, Lady Hardinge Medical College & Associated Hospitals, New Delhi

The revised Terms of Reference of the National AEFI Committee are enclosed.

08/12/20

(Dr. M K Aggarwal)
Additional Commissioner (UIP)

To:

1. Dr. Debashish Choudhary, Director-Professor and Head, Department of Neurology, GB Pant Institute of PGMER, New Delhi – 110002
2. Dr. (Prof.) Neeraj Pandit, Consultant and Head, Department of Cardiology, Room No.- 229
   Main OPD Block, IInd floor, Dr Ram Manohar Lohiya Hospital and PGIMER, Baba Kharag Singh Marg, New Delhi – 110001
3. Dr. Karan Madan, Associate Professor, Department of Pulmonary Medicine and Sleep Disorders, All India Institute of Medical Sciences, Ansari Nagar, New Delhi -110029
4. Dr. Anil Gurtoo, Director-Professor, Department of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
5. Dr. Anju Seth, Director-Professor, Department of Paediatrics, Lady Hardinge Medical College & Associated Hospitals, New Delhi

Copy to:

1. Advisor, National AEFI Committee
2. Chair, National AEFI Committee
3. All members, National AEFI Committee
4. PPS to Secretary, (H&FW)
5. PPS to AS & MD, NHM
6. PPS to AS (MA)
7. PPS to Advisor (RCH)
8. PPS to JC (Imm)

Terms of Reference of the National AEFI Committee

1. Provide technical guidance on policy and implementation to the national AEFI surveillance programme.
2. Update and review AEFI programme guidelines and SOPs and establish systems for ensuring quality data.
3. Provide support for strengthening AEFI surveillance in states through handholding and facilitating training and workshops as and when required.
4. Review the trends of AEFI reports on a regular basis and suggest policy interventions.
5. Review reports of causality assessment from the states and assist states in field investigations, if required.
6. Conduct periodic evaluation of AEFI surveillance in the country.
7. Suggest processes for greater integration of the private sector in the AEFI programme, including reporting, investigation and response.
8. Strengthen integration with the National Pharmacovigilance Programme with partners including CDSCO and Indian Pharmacopoeia Commission.
9. Advice the National AEFI Programme on improved vaccine quality and testing facilities and collaboration with national/international institutions.
10. Suggest issues within AEFI surveillance which require research (operational/implementation) and pilot studies to improve AEFI surveillance.
11. Provide feedback to reporting sites and strengthen AEFI case management and closure.
12. Monitoring the performance of AEFI surveillance system.
13. Conduct causality assessment of reported serious and severe AEFI cases following COVID 19 vaccinations.

Dr. Mahesh Kumar Aggarwal
Additional Commissioner (UIP)
Tel. : 011-23062728, 23062126
E-mail : mk.aggarwal13@nic.in

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली - 110011
GOVERNMENT OF INDIA
MINISTRY OF HEALTH & FAMILY WELFARE
NIRMAN BHAVAN, NEW DELHI - 110011

D. O. No: Z.16025/02/2018-IMM
Dated: 4th January 2021

Dear Mission Directors

Please refer to our earlier letters dated 18 Nov and 22 Dec 2020 in which states were requested to expand the state AEFI committee and include a neurologist, cardiologist, respiratory medicine specialist, medical specialist and an obstetrician-gynaecologist in view of the preparations for strengthening AEFI surveillance for COVID 19 vaccinations.

In this regard, it is proposed to conduct a single batch of online training on investigation and causality assessment of Adverse Event Following Immunization from 08-09 January 2021 from 2:00 pm to 5:30 pm for the new/untrained members of the state AEFI committees.

This is to request you for the following:

1. Nominate 4-6 new members of the AEFI committee for the training on **both the days**
2. Send the names, designations, mobile number and email addresses of the nominated participants in the format at Annexure A to aefiindia@gmail.com with copy to Deepak_polpakara@in.jsi.com **before 05 Jan 2020**.
3. Request the participants to block the dates and time of the training in advance

Correct email addresses are important as the links, tentative agenda and other instructions for the training will be emailed directly to the participants.

With regards

Yours sincerely

Mahesh 04/01/21

(Dr M K Aggarwal)

Mission Director, National Health Mission, All states/UTs

Copy to:

1. Dr S Aneja, Chair, National AEFI Committee
2. SEPIOs, all states/UTs
3. Chairpersons, State AEFI Committees, All states/UTs
4. Dr Pankaj Bhatnagar, Acting Team Lead, WHO-NPSP, New Delhi
5. Dr Vineet Goyal, Focal person (AEFI), WHO-NPSP, New Delhi
6. Dr Deepak Polpakara, Team Lead – AEFI, ITSU
7. All Senior Zonal AEFI Consultants, MOHFW

Annexure A

Training on Causality Assessment of new members of AEFI Committees (states/UTs/national) – 08-09 Jan 2021 (2:00 to 5:30 pm)

List of participants

Name of state/UT:				
S. No.	Name	Designation	Email address	Mobile number
1				
2				
3				
4				
5				
6				

ANNEXURE R/17

Dr. Mahesh Kumar Aggarwal
Additional Commissioner (UIP)
Tel. : 011-23062728, 23062126
E-mail : mk.aggarwal13@nic.in

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली - 110011

GOVERNMENT OF INDIA
MINISTRY OF HEALTH & FAMILY WELFARE
NIRMAN BHAVAN, NEW DELHI - 110011

D. O. No: Z.16025/02/2018-IMM
Dated: 05th January 2021

Dear Colleague

As part of the preparations for strengthening AEFI surveillance for introduction of COVID 19 vaccinations, an online training on investigation and causality assessment of Adverse Event Following Immunization of new members of national and state AEFI committee members is being held on 08 and 09 January 2021 from 2:00 pm to 5:30 pm.

You are requested to make it convenient to attend the training on both these days. The links, tentative agenda and other instructions for the training will be emailed directly to you. Please contact Dr Deepak Polpakara (Deepak_polpakara@in.jsi.com, 9868878721) for clarifications.

Warm Regards,

Yours sincerely

05/01/21

(Dr M K Aggarwal)

To:

1. **Dr. Sujata Mathews, Ram Manohar Lohia Hospital, New Delhi**
2. **Dr. Madhubala Negi, Ram Manohar Lohia Hospital, New Delhi**
3. **Dr. Alka Sharma, Ram Manohar Lohia Hospital, New Delhi**
4. **Dr Rupali Malik, Safdarjung Hospital, New Delhi**
5. **Dr Sameer Gulati, Safdarjung Hospital, New Delhi**
6. **Dr Aparna Agrawal, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
7. **Dr Debashish Chaudhury, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
8. **Dr Anupam Prakash Lady Hardinge Medical College & Associated Hospitals, New Delhi**
9. **Dr Ramesh Agrawal, Lady Hardinge Medical College & Associated Hospitals, N. Delhi**
10. **Dr Ritika Sud, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
11. **Dr Vivek Suman, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
12. **Dr Shubha Laxmi Margekar, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
13. **Dr Priya Bansal, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
14. **Dr Amit Kumar Sharma, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
15. **Dr Sheikh Yasir Islam, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
16. **Dr Shivraj Meena, Lady Hardinge Medical College & Associated Hospitals, New Delhi**
17. **Dr Manish Goyal, Lady Hardinge Medical College & Associated Hospitals, New Delhi**

Copy to:

1. Dr Anju Seth, Chair -Causality assessment sub-committee, National AEFI Committee
2. Dr S Aneja, Chair, National AEFI Committee
3. Dr Anil Gurtoo, Director-professor, Dept. of Medicine, LHMC
4. Dr Deepak Polpakara, Team Lead – AEFI, ITSU
5. All Senior Zonal AEFI Consultants, MOHFW

ANNEXURE R/18

FTS: 3140428
File No. Z.16025/02/2018-IMM
Government of India
Ministry of Health and Family Welfare
Immunization Division
***

Nirman Bhawan, New Delhi
Dated: 11th February, 2021

It has been decided to expand the existing membership of the causality assessment sub-committee at the National level to include medical specialists and community medicine specialists for conducting causality assessment of AEFIs following COVID-19 vaccination with approval of the Secretary, Health and Family Welfare with the following composition:

1. Dr Anil Gurtoo, Director-Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
2. Dr Sujata Mathews, Associate Professor, Dept. of Medicine, Ram Manohar Lohia Hospital, New Delhi
3. Dr Madhubala Negi,Professor, Dept. of Medicine, Ram Manohar Lohia Hospital, New Delhi
4. Dr Alka Sharma, Associate Professor, Dept. of Medicine, Ram Manohar Lohia Hospital, New Delhi
5. Dr Rupali Malik, Associate Professor, Dept. of Medicine, Safdarjung Hospital, New Delhi
6. Dr Sameer Gulati, Associate Professor, Dept. of Medicine, Safdarjung Hospital, New Delhi
7. Dr Aparna Agrawal, Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
8. Dr Debashish Chaudhury, Director Professor and Head of department of Neurology, Govind Ballabh Pant Institute of Post Graduate Medical Education and Research, New Delhi
9. Dr Anupam Prakash, Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
10. Dr Ramesh Agrawal, Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
11. Dr Ritika Sud, Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
12. Dr Vivek Suman, Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
13. Dr Shubha Laxmi Margekar, Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
14. Dr Priya Bansal, Associate Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
15. Dr Amit Kumar Sharma, Associate Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
16. Dr Sheikh Yasir Islam, Associate Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
17. Dr Shivraj Meena, Associate Professor, Dept. of Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi
18. Dr Manish Goyal, Professor, Dept. of Community Medicine, Lady Hardinge Medical College & Associated Hospitals, New Delhi

11/2/21

Dr M K Aggarwal,

Addl. Commissioner (UIP)

To:

All members

Copy to:

1. PPS to Secretary, HFW
2. PPS to AS&MD
3. PPS to AS (MA)
4. PPS to JS (RCH)
5. PPS to Advisor (RCH)
6. PPS to Jt. Commissioner (Immun.)
7. Team Lead-AEFI, ITSU, New Delhi

ANNEXURE R/19

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली - 110011

GOVERNMENT OF INDIA
MINISTRY OF HEALTH & FAMILY WELFARE
NIRMAN BHAVAN, NEW DELHI - 110011

डॉ. मनोहर अगनानी, भा.प्र.से.
अपर सचिव

DR. MANOHAR AGNANI , IAS
Additional Secretary

D.O No. T-13020/03/2021-Imm
Date: 8th April, 2021

Dear Sir,

Reference to this Ministry's Order (enclosed) of even number dated 1st April, 2021 regarding constitution of four sub-groups for expedited causality assessment of serious/severe Adverse Events Following Immunization (AEFI) cases reported following COVID-19 vaccination in a time-bound manner.

The COVID-19 vaccination drive has been going on across all States since 16th January 2021 and as on 7th April, 2021 a total of 8.70 crore doses of COVID-19 vaccines have been administered to beneficiaries and total reported AEFIs cases are 20,650 out of which 735 AEFI cases are under serious/severe category (Death: 238, Hospitalized: 421 & Severe: 76).

In order to sustain confidence of the public and health functionaries on the COVID-19 vaccines and COVID-19 vaccination program, prompt reporting, immediate investigation and time-bound causality of AEFIs is necessary.

Therefore, I would request that the Chairperson of Causality Assessment Sub-committee to ensure that members of these four sub-groups for COVID-19 vaccination should meet and conduct causality assessment of all reported serious/severe AEFI cases in a time-bound manner and direct the AEFI Secretariat to share a bi weekly update with the undersigned in the shared format (annexure) on the progress made by these groups on causality classification of these examined cases.

With kind regards,

Yours sincerely,

Enclosure: as above

(Dr Manohar Agnani)

To

Dr Neeraj Pandit, Professor, Department of Cardiology, Dr RML Hospital & PGIMER, New Delhi

Room No. 145-A, Nirman Bhawan, New Delhi - 110011
Tel. : 011-23061723, E-mail : as-agnani@gov.in

Press Information Bureau **ANNEXURE R/20**
Government of India 440

Ministry of Health and Family Welfare

Bleeding and clotting events following COVID vaccination miniscule in India

National AEFI (Adverse Event Following Immunization) Committee submits report to the Union Health Ministry

Posted On: 17 MAY 2021 2:32PM by PIB Delhi

Bleeding and clotting cases following COVID vaccination in India are minuscule and in line with the expected number of diagnoses of these conditions in the country, a report submitted by the National AEFI (Adverse Event Following Immunization) Committee to the Ministry of Health & Family Welfare said.

Alerts have been raised in some countries on post-vaccination “embolic and thrombotic events” on 11 March 2021 particularly with AstraZeneca-Oxford vaccine [Covishield in India]. A decision was taken to conduct an urgent in-depth analysis of the adverse events (AE) in India in the light of the global concerns.

The National AEFI committee noted that as of 03 April 2021, 75,435,381 vaccine doses had been administered (Covishield – 68,650,819; Covaxin – 6,784,562). Of these, 65,944,106 were first doses and 9,491,275 second dose. Since the COVID-19 vaccination drive was initiated – more than 23,000 adverse events were reported through the CO-WIN platform reported from 684 of the 753 districts of the country. Of these, only 700 cases (@ 9.3 cases /million doses administered) were reported to be serious and severe nature.

The AEFI Committee has completed an in-depth case review of 498 serious and severe events, of which 26 cases have been reported to be potential thromboembolic (formation of a clot in a blood vessel that might also break loose and carried by the blood stream to plug another vessel) events – following the administration of Covishield vaccine – **with a reporting rate of 0.61 cases/ million doses.**

There were no potential thromboembolic events reported following administration of Covaxin vaccine.

AEFI data in India showed that there is a very miniscule but definitive risk of thromboembolic events. The reporting rate of these events in India is around 0.61/million doses, which is much lower than the 4 cases/million reported by UK's regulator Medical and Health Regulatory Authority (MHRA). Germany has reported 10 events per million doses.

It is important to know that thromboembolic events keep occurring in general population as background and scientific literature suggests that this risk is almost 70 per cent less in persons of South and South East Asian descent in comparison to those from European descent.

MOHFW is separately issuing advisories to Healthcare Workers and Vaccine Beneficiaries to encourage people to be aware of suspected thromboembolic symptoms occurring within 20 days after receiving any COVID-19 vaccine (particularly Covishield) and report preferably to the health facility where vaccine was administered:

- breathlessness;
- pain in chest;
- pain in limbs/pain on pressing limbs or swelling in limbs (arm or calf);
- multiple, pinhead size red spots or bruising of skin in an area beyond the injection site;
- persistent abdominal pain with or without vomiting;
- seizures in the absence of previous history of seizures with or without vomiting;
- severe and persistent headache with or without vomiting (in the absence of previous history of migraine or chronic headache);
- weakness/paralysis of limbs or any particular side or part of the body (including face);
- persistent vomiting without any obvious reason;
- blurred vision or pain in eyes or having double vision;
- change in mental status or having confusion or depressed level of consciousness
- Any other symptom or health condition which is of concern to the recipient or the family

Covishield, the COVID-19 vaccine, continues to have a definite positive benefit risk profile with tremendous potential to prevent infections and reduce deaths due to COVID-19 across the world and in India. Over 13.4 crore doses of Covishield vaccine have been administered as on 27 April 2021 in India. MoHFW is continuously monitoring the safety of all COVID-19 vaccines and is promoting reporting of suspected adverse events.

******

MV

Read this release in: Urdu , Marathi , Hindi , Bengali , Assamese , Punjabi , Tamil , Telugu , Kannada , Malayalam

ANNEXURE R/21

Ministry of Health and Family Welfare

COVID19 Vaccination: Myths Vs. Facts

Any death or hospitalization following vaccination cannot be automatically assumed to be due to vaccination

Causality assessments help to understand whether the “Adverse Event Following Immunization” was caused directly due to vaccine, and are conducted at State and national level for the investigated cases

Posted On: 15 JUN 2021 2:51PM by PIB Delhi

There have been some media reports suggesting an increase in the cases of severe AEFI which have also resulted in ‘succumbing of patients’ post vaccination. As per the media reports, 488 deaths following vaccination are linked to post-COVID complications during 16th Jan 2021 and 7th June 2021 period where the total vaccination coverage was 23.5 crore.

It is clarified that these reports are based on incomplete and limited understanding of the matter at hand. It may be noted that the term “succumbed” insinuates causality i.e. the deaths were caused due to vaccination.

The number of deaths reported following COVID-19 vaccination in the country is only 0.0002% of 23.5 crore doses administered which is within the expected death rates in a population. In a population, deaths occur at a certain rate. Crude death rate in 2017 as per SRS data is 6.3 per 1000 persons annually (SRS, Registrar General & Census Commissioner, India from https://main.mohfw.gov.in/sites/default/files/HealthandFamilyWelfarestatisticsinIndia201920.pdf).

It is also important and pertinent to note that the mortality rates for those testing positive for COVID-19 disease is more than 1% and COVID-19 vaccination can prevent these deaths. Therefore, the riskof dying following vaccination is negligible as compared to the known risk of dying due to COVID-19 disease.

Adverse Event Following Immunization (AEFI) is defined as ‘any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. It can be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease’. Healthcare workers, doctors and vaccine recipients have been always

encouraged by the Government of India as well as State Governments to report all deaths, hospitalizations and events resulting in disability as well as any minor and adverse events following immunization at any point of time after vaccination.

Deaths, hospitalizations or events causing disability or concern following any vaccination are categorised as serious or severe cases and are to be investigated at the district level. Causality assessments help to understand whether the event was caused due to the vaccine and are conducted at the state and national level. Therefore, any death or hospitalization following vaccination cannot be automatically assumed to be due to vaccination unless investigated by the AEFI Committees at the district, state and national level and attributed to the Vaccination.

There is a robust system of AEFI surveillance at every level from the district to the State. Once the investigation is completed, the reports are released on the website of the Union health Ministry, following transparent sharing of COVID Vaccination related information.

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