IN THE SUPREME COURT OF INDIA

CIVIL ORIGINAL JURISDICTION

WRIT PETITION (CIVIL) NO. 1220 OF 2021

IN THE MATTER OF:

RACHANA GANGU & ANR. ...PETITIONERS

VERSUS

UNION OF INDIA & ORS. ... RESPONDENTS

AFFIDAVIT DATED 23.11.2022 ON BEHALF OF THE UNION OF INDIA

PAPER-BOOK

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ADVOCATE FOR THE UNION OF INDIA: G S MAKKER

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IN THE SUPREME COURT OF INDIA
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AFFIDAVIT DATED 23.11.2022 ON BEHALF OF THE UNION OF INDIA

I, Dr. Veena Dhawan, Wife of Dr. Puneet Dhawan, aged 57 years, working as Additional Commissioner (immunization) in the Ministry of Health & Family Welfare, Government of India, Nirman Bhawan, New Delhi -110011, the deponent herein, do hereby solemnly affirm and state on oath as under:

1. That I am Additional Commissioner (Immunization) in the Ministry of Health & Family Welfare, Government of India ('MoHFW'). I am filing this affidavit in reply to the present Petition on behalf of the Union of India.

NOTARY K. BANDANA Delhi Regd. No. 19713 Date of Expiry 26.02.2025 GOVT. OF INDIA

23/11/22

(डा. वीना धवन)
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2. At the outset, the answering Respondent offers deep and sincere condolences to the Petitioners on the tragic and untimely demise of their respective daughters. It is most respectfully submitted that the Union of India is deeply sensitive to the concerns raised in the present Petition and the issue of safety in COVID-19 vaccine administration is considered a matter of utmost importance.

3. It is most respectfully submitted that the representations made by the Petitioners vide Prime Minister's Office (PMO) grievance case reference no. PMOPG/E/2021/0442378 and PMOPG/E/2021/0440276 were answered on 10.12.2021 and 31.03.2022 respectively.

True copies of response dated 10.12.2021 and 31.03.2022 to the grievances made by the Petitioners are annexed herewith and marked as **ANNEXURE A1 (Pg no. 41 to 43)** and **ANNEXURE A2 (Pg no. 44 to 47)** respectively.

4. The Petitioners seek the following reliefs from this Hon'ble Court in the present Writ Petition:

NOTARY
K. BANDANA
Delhi
Regd. No. 19713
Date of Expiry
26.02.2025
GOVT. OF INDIA

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i. *Issue a writ of mandamus or any other appropriate writ, order or direction appointing an expert medical board, independent of the Government, to forthwith inquire into and investigate into the deaths of the daughters of Petitioners No. 1 & 2, and to share the report of the autopsy and investigation with the Petitioners in a time-bound manner,*

ii. *Issue a writ of mandamus or any other appropriate writ, order or direction directing the above appointed expert medical board to prepare a protocol for early detection of and timely treatment for the AEFI due to the Covid-19 vaccine such as the ones that led to the deaths of the daughters of Petitioners No. 1 & 2; and*

iii. *Issue a writ of mandamus or any other appropriate writ, order or direction directing the Respondents to grant significant monetary compensation to the Petitioners No. 1 & 2, which will be donated by the Petitioners to organizations working on social issues.*

5. The answering Respondent seeks indulgence of this Hon'ble Court to set out in detail, the entire background of the COVID-19 vaccination program, the decision-making process for administration

NOTARY K. BANDANA Delhi Regd. No. 19713 Date of Expiry 26.02.2025 GOVT. OF INDIA

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of vaccines and the system of monitoring Adverse Effects Following Immunisation (AEFIs) throughout the nation, which will aid an informed adjudication of the issues raised in the present Petition.

6. At the outset it is humbly submitted that the COVID-19 pandemic was an unprecedented challenge for mankind and timely development, manufacturing and administration of vaccines was critical to end the pandemic. In a noted scientific paper in the scientific journal *The Lancet*, it is estimated that vaccines have globally prevented roughly 20 million deaths and in India alone, at least 4 million were estimated to have been prevented with timely access to COVID-19 vaccines.

A true copy of *'Global impact of the first year of COVID-19 vaccination: a mathematical modelling study'* The Lancet Infectious Diseases, dated 22.09.2022 is annexed herewith and marked as **ANNEXURE – A3 (pages 48 to 57).**

7. It is most respectfully submitted that issues raised by the Petitioners fall within the domain of the executive, aided by medical, scientific and other technical experts. Development, testing,

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manufacturing and administration of vaccines, including post administration surveillance and monitoring of AEFIs is a highly technical matter guided by views that emerge from scientific consensus among subject experts. As such, the inquiry of this Hon'ble Court may be limited to whether there is an adequate regulatory mechanism in place and whether the same has been followed.

BRIEF BACKGROUND

8. It is most humbly submitted that the COVID-19 virus is a novel virus and the global landscape of scientific and technical knowledge for this virus is continuously evolving. As soon as the COVID-19 pandemic hit mankind, the Government of India initiated large scale efforts between public and private scientific institutions to ensure that the people of India have early access to vaccines against the COVID-19 virus. This effort resulted in India being one of only a few countries in the world that succeeded in developing and manufacturing vaccines in large quantities indigenously. It may be noted that India has been able meet its vaccination targets on a very aggressive timeline, entirely through domestically produced vaccines. Government of India alongwith State Governments was able to deliver 100 crore vaccine doses in 10 months and 200 crore vaccine doses in 18 months to its

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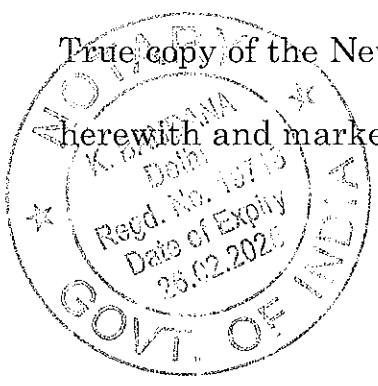
people. This is an unparalleled global achievement and a testament to India's self-sufficiency in vaccine production for its people.

9. India's COVID-19 vaccination drive is based on emerging scientific and epidemiological evidence, WHO guidelines and global best practices. Each vaccine goes through a process of rigorous review by several layers of expert consideration and deliberation both before and after the vaccine is approved for public use as delineated hereunder.

VACCINE APPROVAL AND ADMINISTRATION PROCESS

10. The Drugs and Cosmetics Act, 1940 ('D&C Act') alongwith the Drugs and Cosmetics Rules 1945 ('D&C Rules') regulate the development, manufacture, import, sale and distribution of drugs and cosmetics in the country. Vaccines fall within the definition of 'drug' under Section 3(b) of the Drugs Act. The process of marketing approval for a new drug is governed by the New Drugs and Clinical Trials Rules 2019 ('NDCT Rules')

True copy of the New Drugs and Clinical Trials Rules 2019 is annexed herewith and marked as **ANNEXURE A4 (Pg 58 to 174)**.



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11. The national regulatory agency which approves a new drug for marketing is the Central Drugs Standard Control Organisation ('CDSCO'). The clinical trial and other data for evaluating the application for approval of a new drug is first examined by the Subject Expert Committee (SEC) which is an independent body of experts drawn from across the country from different medical / scientific institutions. The SEC makes a recommendation to the Drugs Controller General of India ('DCGI') and after a further review, the CDSCO grants or rejects the application made by the drug manufacturer. It may be noted that the CDSCO is a globally respected and recognised regulator. CDSCO been assessed by the Bureau of Indian Standards (BIS) and received IS:ISO 9001:2015 certificate for Quality Management System. CDSCO was also assessed by the World Health Organization and given maximum possible marks in its assessment.

A true copy of press release dated 17.02.2017 on WHO assessment of CDSCO is annexed herewith and marked as **ANNEXURE – A5 (pages 175 to 176).**

NOTARY K. BANDANA Delhi Regd. No. 15713 Date of Expiry 25.02.2025 GOVT. OF INDIA

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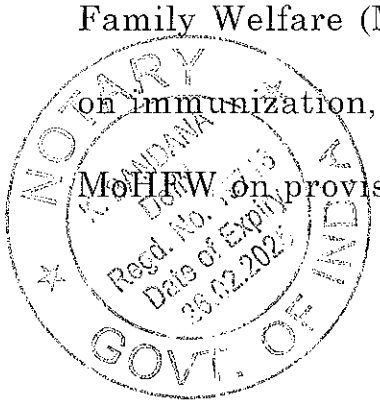
12. In the present case, the respective children of the Petitioners were vaccinated with the Covishield vaccine manufactured by M/s Serum Institute of India. This vaccine went through the same rigorous review of safety and efficacy by independent experts in the SEC before being granted permission for 'restricted use in emergency situation' on 02.01.2021 following which it was included in the National COVID-19 vaccination program which commenced on 16.01.2021. After a further rolling review of clinical trial data as well as AEFI data, the Covishield vaccine was approved for regular use on 27.01.2022.

A true copy of chronology of events for the process of approval for Covishield vaccine is annexed herewith and marked as **ANNEXURE A6 (Pg 177 to 178).**

13. Once a vaccine is given marketing approval by the CDSCO, decisions regarding administering the vaccine are taken with the aid of the National Technical Advisory Group on Immunization ('NTAGI'). NTAGI was established by an order of the Ministry of Health and Family Welfare (MoHFW) in 2001. As India's apex advisory body on immunization, the NTAGI provides guidance and advice to the MoHFW on provision of vaccination and immunization services for



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the effective control of vaccine preventable diseases in the country. The NTAGI is chaired by Secretary, Health & Family Welfare (H&FW) and Co-chaired by Secretary Department of Biotechnology (DBT) and Secretary Department of Health Research (DHR) & Director General Indian Council of Medical Research (ICMR). It also comprises of independent technical experts from medical / scientific institutions across the country such as, immunologists, vaccine and vaccine safety experts, paediatricians, gastroenterologists, public health experts, epidemiologists, vaccination program managers and members from regulatory authorities.

14. The NTAGI is supported by Standing Technical Sub-Committee ('STSC'), which is further supported by two Standing Working Groups: (i) Vaccine Preventable Disease Surveillance; (ii) Immunization and Vaccine Research and Capacity Building. The NTAGI Secretariat provides techno-managerial support for NTAGI work. The work of the Secretariat includes, formulation of policy question to be answered by the working groups, evidence collation and review, risk-benefit analysis, mathematical modeling, VPD surveillance data review, UIP data review, systematic review, primary and

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secondary data analysis, quantitative and qualitative research, policy reports, and public briefing reports.

15. Once the NTAGI Secretariat has compiled the scientific evidence on a particular vaccine, the same is sent to the COVID-19 Working Group which is a body of subject matter experts under NTAGI and has independent experts as well as representatives of ICMR, DBT etc. This group reviews the quality of evidence received from the Secretariat and drafts its recommendations. These recommendations are then sent to the Standing Technical Sub-Committee ('STSC') which is the next body of subject matter experts in the NTAGI hierarchy. The STSC deliberates on the recommendations made by the CWG and forwards its recommendations to the full committee of the NTAGI. The NTAGI then deliberates on recommendations made by the STSC and provides a recommendation to the MoHFW.

True copies of the Code of Practice of NTAGI and NTAGI workflow for COVID-19 vaccines are annexed herewith and marked as **ANNEXURE A7 (Pg 179 to 212)** and **ANNEXURE A8 (Pg 213)** respectively.

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16. To oversee all aspects of COVID-19 vaccination administration, the Government of India constituted the National Expert Group on Vaccine Administration for COVID-19 (NEGVAC). The NEGVAC is the apex advisory body for the National COVID-19 Vaccination Programme and provides the final layer of expert review for recommendations pertaining to COVID-19 vaccination, providing an additional review of recommendations of the NTAGI. After deliberations on the recommendations made by NTAGI, NEGVAC forwards its recommendations to MoHFW. The NEGVAC is chaired by Member (Health) NITI Aayog and co-chaired by Secretary, Ministry of Health and Family Welfare. Its members include Secretaries from the Department of Biotechnology, Department of Health Research, Department of Pharmaceuticals, Ministry of External Affairs, Department of Expenditure, Ministry of Electronics and Information Technology, representatives from five State Governments and technical experts.

17. In *Jacob Puliyel v. Union of India & Ors.* 2022 SCC OnLine SC 533, this Hon'ble Court had the occasion to examine the vaccine approval process of the Government of India in the context of COVID-19 vaccines and held, *"a perusal of the material places on record would*

show that there is material compliance with the procedure prescribed under the Drugs and Cosmetics Act, 1940 and the 2019 Rules, before grant of approval for the emergency use of the two vaccines."

18. In light of the above, it is most respectfully submitted that COVID-19 vaccines, including the Covishield vaccine, have gone through a rigorous regulatory approval process with several layers of independent expert review. The data submitted by the vaccine manufacturer on the safety and efficacy of the said vaccine has been closely examined by various expert bodies as detailed above and continues to be done on a rolling basis. All decisions on vaccine administration are made on the basis of relevant scientific evidence.

ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI) MONITORING, INVESTIGATION, CAUSALITY ASSESSMENT AND INFORMATION DISSEMINATION

19. An Adverse Event Following Immunization ('AEFI') is any untoward medical occurrence that follows immunization of a vaccine recipient. AEFIs are expected to occur in the administration of every vaccine and are continuously monitored by all countries to ensure the safety of vaccination programs. It is critical to note that an AEFI may or may not have a causal relationship with the usage of the vaccine. A

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causal relationship between a vaccine and an AEFI is established by investigation of the AEFI by medical / scientific experts. As such, any AEFI monitoring mechanism broadly has two aspects, i.e. surveillance (to detect the occurrence of AEFIs) and causation analysis (to analyse the safety of the concerned vaccine).

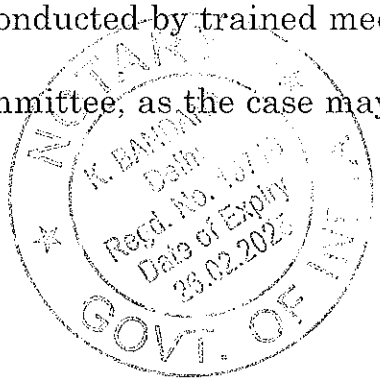
20. India has extensive experience in large scale vaccination and has a robust system of vaccine administration and AEFI surveillance. Even before the COVID-19 pandemic, the Universal Immunization Programme run by Government of India was one of the largest immunization programs in the world. To ensure safe vaccination, over the years a world class AEFI monitoring and investigation system has been created under the National AEFI Secretariat established under the Immunization Technical Support Unit ('ITSU') in 2012.

21. Under this system, AEFI Committees are created at the State and National level which provide guidance to the program and carries out documentation, investigation and causality assessment besides training and orientation of health workers and other involved in AEFI. These committees have clinical experts such as medical specialists, paediatricians, obstetricians / gynaecologists, cardiologists,

neurologists, pathologists, forensic medicine specialists, microbiologists, and also public health specialists, epidemiologists and representatives of the drug regulators. In addition, representatives of professional associations such as Indian Academy of Paediatrics, Indian Medical Association and WHO and UNICEF are also members of the AEFI committees.

A true copy of the Terms of Reference of the National AEFI Committee is annexed herewith and marked as **ANNEXURE A9 (Pg no. 214).**

22. An AEFI can be reported by the vaccine beneficiary, their family / friends, their doctor, or programme administrator on CoWIN or otherwise to the District Immunization Officer ('DIO'). Both Government and private hospitals have been advised to report any suspected cases of AEFI to the DIO. Once the AEFI is reported, it is verified by the DIO as minor, severe or serious under the established protocol. For all severe and serious AEFI cases, causality assessment is conducted by trained medical experts of the State or National AEFI Committee, as the case may be. Once causality assessment results are



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discussed and approved by the National AEFI Committee, the same is uploaded on the MoHFW website.

A true copy of a Flow Chart for reporting of AEFI for COVID-19 is annexed herewith and marked as **ANNEXURE A10 (Pg No. 215).**

23. In order to further strengthen the AEFI reporting mechanism, a strong convergence has been developed with the Pharmacovigilance Programme of India ('PvPI') under the Indian Pharmacopoeia Commission 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 CDSCO is collated and studied in case of any new, previously unknown events identified through AEFI surveillance.

24. The AEFI surveillance system of India was part of the National Regulatory Agency ('NRA') assessment by global experts conducted by WHO in 2017 where the Indian NRA was awarded maximum possible marks in its assessment. **(Ref: ANNEXURE A5)**

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25. Normally vaccination programs are only for the paediatric population. Keeping in view the novel nature of the COVID-19 virus and adults as the initial target population for vaccination, membership of the National AEFI Committee has been expanded to include neurologists, cardiologists, respiratory medicine specialists and other medical specialists. States have also been requested to similarly expand their AEFI committees.

True copies of letters dated 08.12.2020 and 04.01.2021 pertaining to expansion of National and State AEFI Committees are annexed herewith and marked as **ANNEXURE A11 (Pg 216 to 218)** and **ANNEXURE A12 (Pg 219 to 220)** respectively.

26. The COVID-19 vaccination program was started in India on 16.01.2021. In accordance with the priority groups identified by NEGVAC, vaccines were first made available to healthcare workers on 16.01.2021, followed by frontline workers on 01.02.2021, followed by senior citizens (persons above the age of 60 years) and persons aged above 45 years of age with co-morbidities on 01.03.2021. From 01.04.2021 all persons above the age of 45 years were included in the vaccination drive with the same being expanded to cover all persons

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above the age of 18 years from 01.05.2021. At each stage, AEFI data was carefully examined before considering expansion of persons eligible to receive vaccines.

27. Causality assessment of AEFI is one of the most critical facets of AEFI investigation. Causality assessment of AEFI cases is done at the State and National level by experts trained in causality assessment using globally accepted causality assessment checklist, based on the definition and algorithm developed by WHO. The diagnosis of reported cases reported as AEFIs are standardised by the *Brighton Collaboration* with definitions developed through deliberations by independent global experts. Together with the definitions. algorithm and checklist, causality assessments are conducted in line with global standards and best practices. Results of causality assessments done at the state level are conveyed to the national level. At the national level, special sub-groups have been constituted for focused causality assessments of serious and severe AEFI cases on a priority basis. These sub-committees at the national level conduct the causality assessment of all cases. The causality assessment results of each case is then presented to the experts in the National AEFI Committee who discuss the case and may approve the result as assessed by the sub-

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committees, change the results or even send the particular case back for re-investigation / re-assessment or request for more information to form a conclusion on the causality assessment results. 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 on the website of MoHFW. These results are also shared with CDSCO and other stakeholders for appropriate action / policy interventions.

28. For COVID-19 vaccination program, COVID-19 Vaccines Operational Guidelines ('Operational Guidelines') have been developed by MoHFW which set out the AEFI system, management, reporting, investigation and causality assessment protocol.

A true copy of the relevant portion of the COVID-19 Vaccines Operational Guidelines is annexed herewith and marked as **ANNEXURE A13 (Pg 221 to 234).**

29. It is pertinent to note that the Operational Guidelines, which are circulated and explained to all stakeholders in States / UTs, clearly recommend that all vaccination beneficiaries should be

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informed both about the benefits as well as likely side-effects associated with the particular vaccine they choose to take. The Operational Guidelines also state that beneficiaries should be observed at the vaccination session site for at least 30 minutes post vaccination to detect, manage and treat any immediate adverse reactions. State and District authorities (District Immunization Officer / Chief Medical Officer or the Block Medical Officer) have been asked to proactively reach out to all health care service providers such as medical colleges, hospitals (public, autonomous and private) and individual practitioners and sensitise them to report any adverse event following COVID-19 vaccine as per guidelines. Treatment is being provided free of cost in all government health institutions to vaccine beneficiaries who suffer AEFIs. Moreover, posters with information on COVID-19 vaccination, the risks of COVID-19 infection and benefits of vaccination along with rare complications / contraindications associated with vaccines have also been developed in English & Hindi. It has been advised to States/UTs that these posters and other awareness materials should be prominently displayed in all vaccination centres across the country. Awareness has also been created through mass media and social media platforms.

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True copies of posters for COVID-19 vaccination awareness are annexed herewith and marked as **ANNEXURE A14 (Pg 235 to 244).**

30. AEFI surveillance, monitoring and investigation is an ongoing process. Till 19th November 2022, a total of 219.86 crores doses of Covid 19 vaccines have been administered in the country. A total of 92,114 AEFI cases (0.0042 %) have been reported in this period, of which 89,332 (0.0041%) are minor AEFI cases and a total of 2,782 cases are serious and severe AEFIs (0.00013%). However, it may be noted that these figures are prior to causation analysis and any such severe / serious AEFIs including death cannot be attributed to vaccination till the same is causally assessed by the National AEFI Committee.

31. This Hon'ble Court in *Jacob Puliyel* (supra) examined the system of AEFI surveillance in detail and declined to enter into a judicial review of the same:

> *"82. From the material placed before us, we note that the National AEFI Surveillance Secretariat has been functioning for 10 years and as has been pointed out, there is a well-established protocol in place for identification and monitoring of AEFIs. The*

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website of the MoHFW carries the results of causality assessment of AEFI cases, from which the public can obtain relevant information pertaining to AEFIs. We have been informed that a thorough causality assessment analysis of AEFIs is carried out by experts and not every severe disease and death can be attributed to vaccination. Reactions are examined by experts specifically trained to undertake causality analysis before notifying such reactions as adverse events arising from vaccination. There is a well-defined mechanism for collection of data relating to adverse events that occur due to COVID-19 vaccines and the Government of India has taken steps to direct all concerned medical professionals at the ground level to report adverse events. Even medical practitioners at private hospitals are associated with reporting of adverse events. Therefore, we are not inclined to accept the broad-strokes challenge mounted by the Petitioner that the surveillance system of AEFIs in this country is faulty and the correct figures of those who have suffered any side effects, severe reactions or deaths post-inoculation have not been disclosed."

[emphasis supplied]

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CASE OF THE PETITIONERS

32. It is humbly submitted that the AEFI investigation and causality assessment process is a completely transparent process. AEFIs are thoroughly examined and results are made publicly available as soon as possible.

33. In the case of the daughter of Petitioner No. 1, AEFI of Ms. Rithaika Sri Omtri aged 19 years was recorded, reported, investigated and casualty assessment was done by the State and National AEFI Committee. The cause of death has been officially classified by the National AEFI Committee through an AEFI classification as a case of Thrombosis and Thrombocytopenia Syndrome (TTS).

A true copy of Causality assessment results of 178 reported Serious Adverse Events Following Immunization (AEFI) cases following COVID-19 vaccination approved by National AEFI Committee dated 07.12.2021 as uploaded on MoHFW website is annexed herewith and marked as **ANNEXURE A15 (Pg 245 to 251).**

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34. After introduction of the Covishield vaccine for vaccination against COVID-19 in various countries, TTS was identified as an AEFI in a few European countries. In addition, after examining the Indian AEFI data, the MoHFW issued an advisory for healthcare workers as well as other stakeholders for awareness among medical professionals and vaccine beneficiaries of TTS as a possible AEFI, stating that there was 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 4 cases/million reported by UKs Regulator Medical and Health Regularly Authority (MHRA)."*

An advisory to this effect was also issued by the Press Information Bureau on 17.05.2021. Another advisory to States / UTs was issued on 11.10.2021 to encourage more reporting of such AEFIs and for creating more awareness of TTS as a possible AEFI of the Covishield vaccine. However, it may be noted that the occurrence of TTS as an AEFI was and still is a very rare event, at a far less frequency than that observed in Europe. This is not unusual as different populations react differently to different vaccines due to genetic variations.

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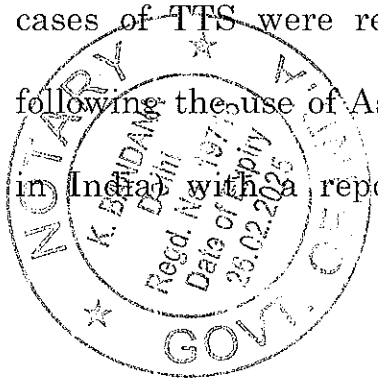
It is also respectfully submitted that the information about TTS as an AEFI has been included in the package insert / summary of product characteristics of Covishield which is available inside the packaging of the vaccine as well as on the website of the vaccine manufacturer.

True copies of letter dated 17.05.2021, PIB release dated 17.05.2021 and letter dated 11.10.2021 are annexed herewith and marked as **ANNEXURE A16 (Pg 252 to 258)** and **ANNEXURE A17 (Pg 259 to 260)** and **ANNEXURE A18 (Pg no. 261)** respectively.

35. It may be noted that as on 30.09.2022, there have been a total of 26 AEFI cases of TTS reported in India, out of which in 14 cases, the individual recovered after hospitalisation and in 12 cases the individual passed away. The reporting rate of TTS in India is 0.001 per one lakh doses administered, making it an extremely rare event.

36. The rate of reporting of TTS as an AEFI in other nations is also pertinent to note. In Canada, as of August 2022, a total of 105 AEFI cases of TTS were reported among which 64 cases were reported following the use of AstraZeneca vaccine (administered as Covishield in India) with a reporting rate of 2.27 cases per one lakh doses



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administered. In Australia, as of July 2022, 173 AEFI cases of TTS have been reported following the use of the AstraZeneca vaccine with a reporting rate of 1.66 cases per one lakh doses administered. In the United Kingdom, as of August 2022, a total of 39 AEFI cases of TTS following the use of AstraZeneca vaccine have been reported with a reporting rate of 0.06 cases per one lakh doses administered.

37. In the case of the daughter of Petitioner No. 2, the AEFI of Ms. Karunya Venugopalan, aged 20 years was recorded, reported, investigated and casualty assessment was done by the State and National AEFI Committee. The cause of death has been officially classified by the National AEFI Committee through an AEFI classification as '*B1 - Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event*' with a diagnosis of Multisystem Inflammatory Syndrome of Children (MIS-C).

A true copy of Causality assessment results of 22 reported Serious Adverse Events Following Immunization (AEFI) cases following COVID19 Vaccination approved by National AEFI Committee dated

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05.11.2021 as uploaded on MoHFW website is annexed herewith and marked as **ANNEXURE A19 (Pg 262 to 264).**

38. As per *Brighton Collaboration*, Multisystem inflammatory syndrome in children/adults (MIS-C/A) is identified as an Adverse Event of Special Interest (AESI) following COVID-19 vaccination. As it is a rare but serious health condition associated with COVID-19, it is recommended that such event be recorded and evaluated by the pharmacovigilance bodies reviewing the adverse event due to COVID-19 vaccines. However, as of now, there is no definitive evidence globally to associate MIS C/A with COVID-19 vaccines and no causal association of MIS C/A has been proven with COVID-19 vaccines. The Pharmacovigilence Risk Assessment Committee of the European Medicines Agency has also concluded that there is currently insufficient evidence on a possible link between COVID-19 vaccines and very rare cases of MIS C/A. However, MIS C/A is still being considered an Adverse Event of Special Interest (AESI) and is being monitored accordingly. The National AEFI Committee is alert to cases of MIS C/A and such events are being captured and evaluated/assessed as per the *Brighton Collaboration* definitions.

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Therefore, as per global scientific consensus, MIS is currently classified as an AESI and not an AEFI and there is no definitive evidence to conclude a causal relationship with COVID-19 vaccinations.

A true copy of *Brighton Collaboration's* COVID-19 AESIs available at [https://brightoncollaboration.us/wp-content/uploads/2021/01/COVID-19-updated-AESI-list.pdf] is annexed herewith and marked as **ANNEXURE A20 (Pg 265 to 266).**

39. From the above facts, it is evident that the existing mechanism for monitoring, investigation and analysis of AEFIs is adequate, effective and transparent. The prayers made by the Petitioners in regard to an independent review of AEFI cases ought not to be granted by this Hon'ble Court as the same would plant a seed of doubt in the existing regulatory and AEFI monitoring mechanism and harm public interest. It may be noted that the Petitioners have failed to show how the existing AEFI monitoring and investigation system has proven to be inadequate in the present case.

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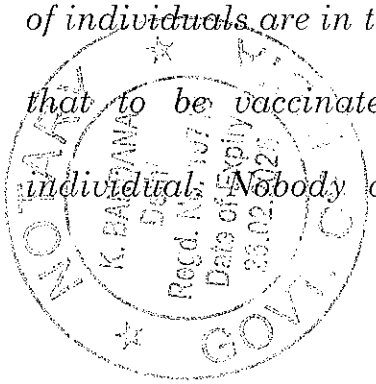
INFORMED CONSENT

40. It is stated by the Petitioners that informed consent was not taken before vaccination. This is an incorrect / misleading submission not supported by any material on record and the following submissions may be appreciated in this regard.

41. It is critical to appreciate that vaccination of eligible population under the National Covid-19 Vaccination Program is voluntary. The Operational Guidelines issued by the Central Government to all States/UTs clearly state that vaccination is voluntary.

42. In *Jacob Puliyel* (supra) this Hon'ble Court noted the voluntary nature of the National COVID-19 Vaccination Program and held as under:

> *"41. Before dealing with the issue of coercive vaccination, it is necessary to consider whether the right of privacy of individuals can override public health, more so, when the submission on behalf of the Respondents is that steps taken to restrict the rights of individuals are in the larger interest of public health. It is true that to be vaccinated or not is entirely the choice of the individual. Nobody can be forcefully vaccinated as it would*



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result in bodily intrusion and violation of the individual's right to privacy, protected under Article 21 of the Constitution of India. Personal autonomy was read into Article 21 by this Court in Common Cause (supra), by placing reliance on National Legal Services Authority v. Union of India, and Aruna Ramachandra Shanbaug (supra). This Court, in Common Cause (supra), emphasized the right of an individual to choose how he should live his own life, without any control or interference by others. It recognised the right of an individual to refuse unwanted medical treatment and to not be forced to take any medical treatment that is not desired. In view of the categoric statement of the Union of India that vaccination of COVID-19 is voluntary, the question of any intrusion into bodily integrity does not arise for consideration in this case."

[emphasis supplied]

43. It is most respectfully submitted that the concept of informed consent is inapplicable to the voluntary use of a drug such as a vaccine. While the Government of India strongly encourages all eligible persons to undertake vaccination in public interest, there is no legal compulsion for the same. As detailed earlier, all relevant

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information on COVID-19 vaccination is made freely available in public domain by both the vaccine manufacturer and MoHFW. Just as a medicine has side effects, AEFIs are reported for every vaccine in the world. A vaccine beneficiary always has the option to access even more information about the vaccine and its possible adverse effects from the health workers at the vaccination site or their doctor before making an informed decision on their own. As such, it is humbly submitted that once a vaccine beneficiary who has access to all relevant information, voluntarily chooses to enter a vaccination center and receive vaccination, the question of a lack of informed consent does not arise.

COMPENSATION

44. The Petitioners have sought compensation from the Respondents on the death of their respective children. As stated above, causation analysis has revealed that the death of daughter of Petitioner No. 1 was from a vaccine product related reaction while in the case of daughter of Petitioner No. 2, there is insufficient evidence to arrive at a definitive conclusion.

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45. A claim for compensation for AEFI cases may arise at two stages, viz. during the conduct of clinical trial for the vaccine (vaccine development stage) or after marketing authorization has been obtained from the Government of India and the vaccine is being administered to the public (vaccine administration stage).

46. During the vaccine development stage, when a clinical trial is being conducted, if a trial participant suffers from any physical injury or death from an AEFI, the sponsor of the clinical trial (normally the vaccine manufacturer) is under a legal obligation to provide free treatment to the trial participant in case of injury and in case of the trial participant's death, financial compensation to their legal heir. The same is provided for under Chapter VI of the NDCT Rules. This provision has been made to safeguard the interests of clinical trial participants who take a higher degree of risk at the drug development stage when the drug is still experimental, in the interest of mankind. It may be kept in mind that without such persons volunteering for clinical trials, the drug development process would be adversely affected.

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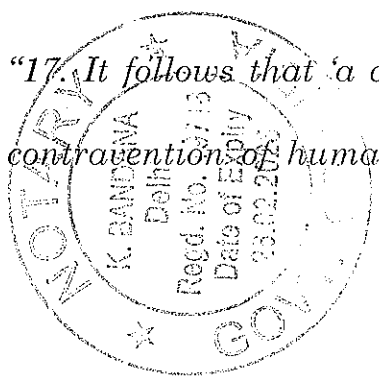
47. At the vaccine administration stage, after marketing authorization has been obtained from the Government of India and the vaccine is available to the public, if a person suffers physical injury or death from an AEFI, appropriate remedies in law are open to the vaccine beneficiary or their family including approaching civil courts for a claim of damages / compensation for negligence, malfeasance or misfeasance. Such claims may be determined on a case-to-case basis in an appropriate forum.

48. Another aspect on the prayer for compensation ought to be considered by this Hon'ble Court. It is pertinent to note that the Petitioners have approached this Hon'ble Court under Article 32 of the Constitution, seeking compensation from the Union of India.

49. An illuminating exposition of law on award of compensation from the State in public law proceedings was made in *Nilabati Behera v. State of Orissa and Ors.* (1993) 2 SCC 746, where a three-judge bench of this Hon'ble Court held:

"17. It follows that 'a claim in public law for compensation' for contravention of human rights and fundamental freedoms, the



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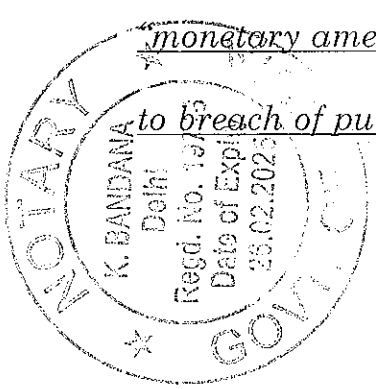
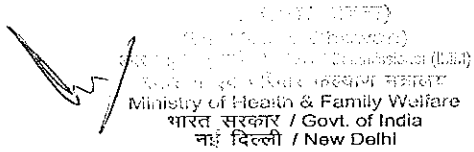
protection of which is guaranteed in the Constitution, is an acknowledged remedy for enforcement and protection of such rights, and such a claim based on strict liability made by resorting to a constitutional remedy provided for the enforcement of a fundamental right is 'distinct from, and in addition to, the remedy in private law for damages for the tort' resulting from the contravention of the fundamental right. The defence of sovereign immunity being inapplicable, and alien to the concept of guarantee of fundamental rights, there can be no question of such a defence being available in the constitutional remedy. It is this principle which justifies award of monetary compensation for contravention of fundamental rights guaranteed by the Constitution, when that is the only practicable mode of redress available for the contravention made by the State or its servants in the purported exercise of their powers, and enforcement of the fundamental right is claimed by resort to the remedy in public law under the Constitution by recourse to Articles 32 and 226 of the Constitution..."

34. The public law proceedings serve a different purpose than the private law proceedings. The relief of monetary

compensation, as exemplary damages, in proceedings under Article 32 by this Court or under Article 226 by the High Courts, for established infringement of the indefensible right guaranteed under Article 21 of the Constitution is a remedy available in public law and is based on strict liability for contravention of the guaranteed basic and indefensible rights of the citizen. The purpose of public law is not only to civilise public power but also to assure the citizen that they live under a legal system which aims to protect their interests and preserve their rights. Therefore, when the court moulds the relief by granting "compensation" in proceedings under Article 32 or 226 of the Constitution seeking enforcement or protection of fundamental rights, it does so under the public law by way of penalising the wrongdoer and fixing the liability for the public wrong on the State which has failed in its public duty to protect the fundamental rights of the citizen. The payment of compensation in such cases is not to be understood, as it is generally understood in a civil action for damages under the private law but in broader sense of providing relief by an order of making "monetary amends" under the public law for the wrong done due to breach of public duty, of not protecting the fundamental rights





of the citizen. The compensation is in the nature of "exemplary damages" awarded against the wrongdoer for the breach of its public law duty and is independent of the rights available to the aggrieved party to claim compensation under the private law in an action based on tort, through a suit instituted in a court of competent jurisdiction or/and prosecute the offender under the penal law."

[emphasis supplied]

50. In essence, this Hon'ble Court has held that an award for compensation from the State in a proceeding under Article 32 or 226 of the Constitution is a remedy available in public law based on strict liability for contravention of fundamental rights made by the State. The Union of India along with the various State / UT Governments have only administered the National COVID-19 Vaccination Program. The vaccines in use under the vaccination program are manufactured by third parties and have successfully undergone thorough regulatory review in India as well as other nations, being recognised globally as safe and effective. In these facts, it is most humbly submitted that holding the State directly liable to provide compensation under the narrow scope of strict liability for extremely rare deaths occurring due

to AEFIs from the use of vaccines may not be legally sustainable. In fact, the facts placed above show how the Union of India has made substantial efforts in ensuring a safe and effective vaccination program against COVID-19 in the middle of a highly challenging situation presented by the COVID-19 pandemic.

CONCLUSION

51. The facts placed in this affidavit show:

51.1 The regulatory approval process for vaccines under the D&C Act and Rules is a well-established, internationally recognised system with several layers of independent expert review for safety and efficacy.

51.2 Once a vaccine has been approved for use by the CDSCO, a detailed examination of scientific evidence and data is conducted by the NTAGI which makes its recommendations on use/administration of vaccines after several layers of independent expert review on safety and efficacy of vaccines.

51.3 For COVID-19 vaccines, recommendations of the NTAGI undergo another layer of expert review by the NEGVAC after which final recommendations on use and administration of COVID-19 vaccines are placed before MoHFW for approval.

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51.4 This Hon'ble Court in *Jacob Puliyel (supra)* has held that for regulatory approval of COVID-19 vaccines, there was material compliance with the provisions of the D&C Act and Rules. In other words, the regulatory process envisaged under the statutory scheme has been followed. This includes the vaccine Covishield with which the respective children of the Petitioners were vaccinated.

51.5 The existing mechanism for monitoring, investigation and analysis of AEFIs under the National AEFI Committee and Secretariat is adequate, effective, transparent, guided by global best practices and scientific / medical experts. The prayers made by the Petitioners in regard to an independent review of AEFI cases ought not to be granted by this Hon'ble Court as the same would plant a seed of doubt in the existing regulatory and AEFI monitoring mechanism and harm public interest. It may be noted that the Petitioners have failed to show how the existing AEFI monitoring and investigation system has proven to be inadequate in the present case.

51.6 This Hon'ble Court in *Jacob Puliyel* (supra) examined the system of AEFI surveillance in detail and declined to enter into a judicial review of the same.

NOTARY K. BANDANA Delhi Regd. No. 19713 Date of Expiry 26.02.2025 GOVT. OF INDIA

(डॉ. वीना धवन)
(Dr. Veena Dhavan)
अपर आयुक्त (इम्यु) / Additional Commissioner (IMM)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
Ministry of Health & Family Welfare
भारत सरकार / Govt. of India
नई दिल्ली / New Delhi

51.7 AEFI causation analysis as approved by the National AEFI Committee has revealed that the death of daughter of Petitioner No. 1 was TTS which was found to be a vaccine product related reaction while in the case of daughter of Petitioner No. 2, the cause of death was MIS and there is insufficient evidence to arrive at a definitive conclusion on causation.

51.8 TTS is classified as an AEFI, while MIS is classified as an AESI. Both are being monitored closely by the National AEFI Committee. Requisite information and advisories on TTS as a possible AEFI have been placed in public domain by both the MoHFW and the vaccine manufacturer.

51.9 The concept of informed consent is inapplicable to the voluntary use of a drug such as a vaccine inasmuch as there is no legal compulsion for the same. All relevant information on COVID-19 vaccination is made freely available in public domain by both the vaccine manufacturer and MoHFW. Further, a vaccine beneficiary has the option to access more information about the vaccine and its possible adverse effects from the health workers at the vaccination site or their doctor before making an informed decision on their own. As such, once a vaccine

beneficiary who has access to all relevant information, voluntarily chooses to enter a vaccination center and receive vaccination, the question of a lack of informed consent does not arise.

51.10 If a person suffers physical injury or death from an AEFI, appropriate remedies in law are open to the vaccine beneficiary or their family including approaching civil courts for a claim of damages/compensation for negligence, malfeasance or misfeasance. Such claims may be determined on a case-to-case basis in an appropriate forum.

51.11 There is no material to suggest how the State can be fastened with strict liability for the tragic death of the respective children of the Petitioners which is the requirement in law to sustain a claim for compensation against the State under Article 32 of the Constitution. To the contrary, the facts placed in this affidavit show how the Government of India has made substantial efforts in ensuring a safe National COVID-19 Vaccination Program.

NOTARY K. BANDANA Delhi Regd. No. 19713 Date of Expiry 26.02.2025 GOVT. OF INDIA

52. In light of the above submissions, it is most respectfully submitted that the prayers made by the Petitioners cannot be granted

(डॉ. वीना धवन)
(Dr. Veena Dhawan)
अवर आयुक्त (इम्यू) / Additional Commissioner (IMM)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
Ministry of Health & Family Welfare
भारत सरकार / Govt. of India
नई दिल्ली / New Delhi

by this Hon'ble Court and the answering Respondent prays that the present Writ Petition be dismissed.

53. The present affidavit is filed bona fide and in the interest of justice.

23/11/22

DEPONENT

(डॉ. वीना धवन)
(Dr. Veena Dhawan)
अपर आयुक्त (इम्यू.) / Additional Commissioner (IMM)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
Ministry of Health & Family Welfare
भारत सरकार / Govt. of India
नई दिल्ली / New Delhi

VERIFICATION

I, the deponent above named, do hereby verify that the contents of Para 1 to 53 of my above affidavit are prepared on the basis of instructions received by me and on the basis of legal advice received and no part of it is false and nothing material has been concealed therefrom to the best of my knowledge.

Verified at New Delhi on this 23 NOV 2022

IDENTIFIED
Nitesh Jain
MAH/4339/2016

NOTARY PUBLIC DELHI
K. BANDANA
Delhi
Regd. No. 19713
Date of Expiry
28.02.2023
GOVT. OF INDIA

23 NOV 2022

ATTESTED
NOTARY PUBLIC DELHI
GOVT. OF INDIA
Mob.: 9654768498

23/11/22

DEPONENT

(डॉ. वीना धवन)
(Dr. Veena Dhawan)
अपर आयुक्त (इम्यू.) / Additional Commissioner (IMM)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
Ministry of Health & Family Welfare
भारत सरकार / Govt. of India
नई दिल्ली / New Delhi

41 Annexure-A1

Details for registration number : PMOPG/E/2021/0440276

Name	Rachana Gangu
Date of receipt	14/07/2021
Address	Villa A37 Dewsville Manchirevula, Rd next to M.S.Royal Function Hall
District name	Hyderabad
State name	Telangana
Mobile no	9573151818
Email Id	RachanaGangu@gmail.com

Grievance description

Namaste Dear Modi Ji,

I am writing to you as a mother who lost her beloved 18yr old daughter. My daughter Rithaika Omtri was an active kid who was aspiring to become an architect. She was a victim of adverse side effect of Covishield vaccine. I am writing to you from Hyderabad, Telangana, so my voice can be heard and no other innocent lives are lost. Like many others, we believed in science, and we believed in the vaccines, and got my daughter her first dose of Covishield on May 29th 2021. But within a week of receiving the vaccine she developed adverse side effects and had CVST (Cerebral Venous Sinus Thrombosis) which caused blood clots and massive brain hemorrhage. In spite of having an emergency surgery, medical care and trying out all available options, her life couldn't be saved and we lost her on 19th June 2021. Prior to this, she was a healthy girl with no medical issues. We cannot explain the agony we are going through for having lost our healthy daughter. We are writing to you in the hope of preventing another parent from experiencing similar pain.

After the passing of my daughter, we have been hearing of many more cases of blood clots happening here in our country. This complication has been reported from a number of countries using AstraZeneca Vaccine - Covishield (AZD1222) such as the UK, European Union, and Scandinavian countries. The majority of affected patients thus far are women under the age of 50years, and it seems to occur 4 to 20 days after vaccination. Based on our online research and literature review we were able to gather the following facts. As per the UK's Medicines and Healthcare Products Regulatory Agency, atleast 79 reports of thrombosis associated with low platelets were reported by 31 March 2021, of which 44 were CVST. Of these 79 cases, 51 were in women and 28 in men. All of the UK cases have occurred after the first dose. The risk was higher in the younger age groups, those aged 18-29 years. The agency concluded that while in most adult age groups, the benefits of the AstraZeneca vaccine outweigh the risks except for in the younger 18-29 year age group, for which the risk-benefit equation is more finely balanced and the risk of CVST was disproportionately higher.

We are very concerned about the lack of education about potential side effects being given to recipients. If we had known about this side effect, we could've watched out for the symptoms and an early medical intervention could have saved my daughter's life. While as a government public health policy, the need to vaccinate a large population might take priority, we request you to kindly consider modification of the guidelines based on the side effects experience gathered both in India and Europe. The data so far has shown a significantly higher risk of blood clots for women under the age of 50.

As the vaccination rates are increasing, it is inevitable that a higher number of younger age group people will be at risk for blood clots. These side effects could potentially cost the lives of healthy individuals who would likely have survived the COVID-19 infection. In the long-term, serious vaccine side effects could cause greater distrust in vaccine efficacy and erode people's trust in vaccination. Instead, if the people most vulnerable to blood clots from Covishield (women under the age of 50) are offered Covaxin vaccine, overall the risk to individuals can be reduced. We humbly request you to look into this matter and consider changing the vaccine recommendations.

We need to have safety management protocols in place. We need to look into advocacy and awareness of Vaccine Induced complications for healthcare professionals, so they can be prepared to act quickly with proper treatment.

I request you to consider this issue with high priority. We are ready to provide any further details needed.

Thank you for your attention to the voice of a mother in agony.

Humble Salutations,
Rachana Gangu

Additional Information	Not Provided
Type of receipt	Transferred

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ATR Details for registration number : PMOPG/E/2021/0440276

Grievance Officer Name	Sachin Kumar
Grievance Officer Designation	Deputy Secretary
Organisation Name	Covid Vaccination
Nature of Grievance	AEFI
Citizen's Demand	Other
Resolution Done	Other
Cause of Grievance	Other
Resolution Type	Fully Resolved
Date on Action Initiated for Resolution	31/03/2022
Resolution Date	31/03/2022

Remarks

The sad demise of your daughter is irreparable. However, with regard to the above grievance, it is informed that all minor, serious and severe Adverse Event Following Immunization (AEFI) following CoVID 19 vaccinations are reported by vaccinators and district immunization officers through the Co-WIN portal. Serious and severe AEFIs (deaths, hospitalizations and cases occurring in clusters or which raise parental/community concern) are investigated. In death cases, all hospital records, past treatment records, post mortem reports/ verbal autopsy reports, etc. are collected. Causality assessment of all serious and severe cases are conducted at the state and national levels.

As we are aware that COVID Vaccination is voluntary. In case of any causality due to covid vaccination, the Health Department or vaccine manufacturer shall not be hold responsible for any loss of life after vaccination. The Government of India has given clearance for administrating covid vaccines on the basis of review of available scientific evidences, global examples and the practices being followed in other countries implementing COVID-19 vaccination.

Action History of registration number: PMOPG/E/2021/0440276

SN.	Action Taken	Date of Action	From	To	Remarks	Action Taken by	Document
1	RECEIVED THE GRIEVANCE	14/07/2021	COMPLAINANT - (C1TZN)	Prime Ministers Office - (PMOPG)			
2	TAKEN UP WITH SUBORDINATE ORGANISATION	14/07/2021	Prime Ministers Office - (PMOPG)	Department of Health & Family Welfare - (DHLTH)	Please take necessary action.		
3	TAKEN UP WITH SUBORDINATE ORGANISATION	16/07/2021	Department of Health & Family Welfare - (DHLTH)	Covid Vaccination - (DSCVD)		Shri Alok Saxena (Additional Secretary)	
4	CASE DISPOSED OF	31/03/2022	Covid Vaccination - (DSCVD)	COMPLAINANT - (C1TZN)	The sad demise of your daughter is irreparable. However, with regard to the above grievance, it is informed that all minor, serious and severe Adverse Event Following Immunization (AEFI) following CoVID 19 vaccinations are reported by vaccinators and district immunization officers through the Co-WIN portal. Serious and severe AEFIs (deaths, hospitalizations and cases occurring in clusters or which raise parental/community concern) are investigated. In death cases, all hospital records, past treatment records, post mortem reports/ verbal autopsy reports, etc. are collected. Causality assessment of all serious and severe cases are conducted at the state and national levels. As we are aware that COVID Vaccination is voluntary. In case of any causality due to covid vaccination, the Health Department or vaccine manufacturer shall not be hold responsible for any loss of life after vaccination. The Government of India has given clearance for administrating covid vaccines on the basis of review of available scientific evidences, global examples and the practices being followed in other countries implementing COVID-19 vaccination.	Sachin Kumar (Deputy Secretary)	

Print ✖ Close

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Annexure- A2

Details for registration number : PMOPG/E/2021/0442378

Name	Venugopalan Govindan
Date of receipt	16/07/2021
Address	Karunyam, EB Colony, Vadavalli
District name	Coimbatore
State name	Tamilnadu
Mobile no	9894065066
Email Id	gvenugopalan@gmail.com

Grievance description

Namaste PM ji.

I lost my healthy daughter to COVID Vaccination related complications, some details of which are available in my change.org petition

http://www.change.org/p/health-minister-post-vaccination-mis-a-awareness-and-antibody-testing-required

Among the visitors I get who come to grieve with us, many are saying such events from their places also. I think this needs to be investigated and a database built.

Perhaps the vaccince that is formulated for a 45 year old male isn't quite suitable for a 20 year old female who already has significant antibodies in her body.

Add to that the lack of knowledge in general at the medical fraternity about MIS-A, it's diagnosis and treatment protocol.

I urge your good office to look into this with due consideration and gather data (which I am certain now is non-existent. If you ask now how many people died within 2 months after taking vaccine, I don't think we have such data)

We need to save young lives. Look forward to your positive action Sir. I shall be more than happy to provide any and all information and fully cooperate to ensure that no other parent lands in my state.

Bharat Mata Ki Jai!
Vande Mataram

Venugopalan.G

Additional Information	Not Provided
Type of receipt	Transferred

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Action History of registration number: PMOPG/E/2021/0442378

SN.	Action Taken	Date of Action	From	To	Remarks	Action Taken by	Document
1	RECEIVED THE GRIEVANCE	16/07/2021	COMPLAINANT - (C1TZN)	Prime Ministers Office - (PMOPG)			
2	TAKEN UP WITH SUBORDINATE ORGANISATION	16/07/2021	Prime Ministers Office - (PMOPG)	1. DHLTH - Department of Health & Family Welfare, 2. GOVTN - Government of Tamil Nadu			
3	TAKEN UP WITH SUBORDINATE ORGANISATION	16/07/2021	Department of Health & Family Welfare - (DHLTH)	Covid Vaccination - (DSCVD)		Shri Alok Saxena (Joint Secretary)	
4	TAKEN UP WITH SUBORDINATE ORGANISATION	30/09/2021	Government of Tamil Nadu - (GOVTN)	District Collectorate CBE - (CB01D)		cmcell (ASO)	
5	CASE DISPOSED OF	10/12/2021	District Collectorate CBE - (CB01D)	COMPLAINANT - (C1TZN)	Petition accepted and the solution for the grievence is given in the attachment	Dist Collector (Dist Collector)	

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Translation

Municipal Administration and Water Supply Department

Sender

Chief Municipal Officers

Coimbatore Corporation

Coimbatore, 641001

Recipient

Mr. Venugopalan Kovithan

Karunyam EB Coloy

Vadavalli, Combatore

NAKAN 6453/202ME31 10/2021

1.	To Prime Minister Sent Petition No. and Day	PMOPG/E/2021/0440276 Date 16.07.2021
2.	Name of Petitioner and address	Mr. Venugopalan Kovindan Karunyam EB Coloy Vadavalli, Coimbatore
3.	Details of the request	Regarding advice on Covid-19 Vaccination
4.	Details of action taken	Presently, Coimbatore Municipal Corporation provides for Covid-19 vaccination services and vaccination for 1st and 2nd dose is going on intensively. So, inquire to get vaccinated in nearby centre.
5.	Send to the petitioner	As per serial no. 4
6.	Is the request accepted? Or rejected?	Accepted
7.	Request rejected, if so, the reason	

Accreditation Officer

Coimbatore Municipal Corporation

47

Translation

Municipal Administration and Water Supply Department

Sender

Chief Municipal Officers

Coimbatore Corporation

Coimbatore, 641001

Recipient

Mr. Venugopalan Kovithan

Karunyam EB Coloy

Vadavalli, Combatore

NAKAN 6453/202ME31 10/2021

1.	To Prime Minister Sent Petition No. and Day	PMOPG/E/2021/0442378 Date 11.07.2021
2.	Name of Petitioner and address	Mr. Venugopalan Kovindan Karunyam EB Coloy Vadavalli, Coimbatore
3.	Details of the request	Regarding advice on Covid-19 Vaccination
4.	Details of action taken	Covid1-9 Vaccination grievance is under review. Moreover, related to this matter is well under taken by the Government of Tamil Nadu.
5.	Send to the petitioner	As per serial no. 4
6.	Is the request accepted? Or rejected?	Accepted
7.	Request rejected, if so, the reason	

Accreditation Officer

Coimbatore Municipal Corporation

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From Tamil to English

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48 Annexure-A3

Global impact of the first year of COVID-19 vaccination: a mathematical modelling study

The first COVID-19 vaccine outside a clinical trial setting was administered on Dec 8, 2020. To ensure global vaccine equity, vaccine targets were set by the COVID-19 Vaccines Global Access (COVAX) Facility and WHO. However, due to vaccine shortfalls, these targets were not achieved by the end of 2021. We aimed to quantify the global impact of the first year of COVID-19 vaccination programmes.

A mathematical model of COVID-19 transmission and vaccination was separately fit to reported COVID-19 mortality and all-cause excess mortality in 185 countries and territories. The impact of COVID-19 vaccination programmes was determined by estimating the additional lives lost if no vaccines had been distributed. We also estimated the additional deaths that would have been averted had the vaccination coverage targets of 20% set by COVAX and 40% set by WHO been achieved by the end of 2021.

Based on official reported COVID-19 deaths, we estimated that vaccinations prevented 14·4 million (95% credible interval [CrI] 13·7–15·9) deaths from COVID-19 in 185 countries and territories between Dec 8, 2020, and Dec 8, 2021. This estimate rose to 19·8 million (95% CrI 19·1–20·4) deaths from COVID-19 averted when we used excess deaths as an estimate of the true extent of the pandemic, representing a global reduction of 63% in total deaths (19·8 million of 31·4 million) during the first year of COVID-19 vaccination. In COVAX Advance Market Commitment countries, we estimated that 41% of excess mortality (7·4 million [95% CrI 6·8–7·7] of 17·9 million deaths) was averted. In low-income countries, we estimated that an additional 45% (95% CrI 42–49) of deaths could have been averted had the 20% vaccination coverage target set by COVAX been met by each country, and that an additional 111% (105–118) of deaths could have been averted had the 40% target set by WHO been met by each country by the end of 2021.

COVID-19 vaccination has substantially altered the course of the pandemic, saving tens of millions of lives globally. However, inadequate access to vaccines in low-income countries has limited the impact in these settings, reinforcing the need for global vaccine equity and coverage.

Schmidt Science Fellowship in partnership with the Rhodes Trust; WHO; UK Medical Research Council; Gavi, the Vaccine Alliance; Bill & Melinda Gates Foundation; National Institute for Health Research; and Community Jameel.

Lancet Infect Dis 2022; 22: 1293–302

Published June 23, 2022
https://doi.org/10.1016/S1473-3099(22)00320-6

See ... page 1254

*Contributed equally

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Correspondence to: Dr Oliver J Watson, MRC Centre for Global Infectious Disease Analysis, Imperial College London, London W2 1PG, UK o.watson15@imperial.ac.uk

The first COVID-19 vaccine was delivered outside of a clinical trial setting on Dec 8, 2020.[1] By Dec 8, 2021, 55·9% of the global population was estimated to have received at least one dose of a COVID-19 vaccine, 45·5% estimated to have received two doses, and 4·3% estimated to have received a booster dose.[2] Despite the incredible speed with which COVID-19 vaccines were developed in 2020 and subsequently distributed during 2021, more than 3·5 million deaths due to COVID-19 have been reported globally since the first vaccine was administered.[2]

Understanding the global impact of vaccination on the course of the COVID-19 pandemic is challenging given the heterogeneous access to vaccines coupled with different levels of transmission and ongoing non-pharmaceutical interventions across countries. In the early months of 2021, the impact of vaccination would have been minimal because of the delay in developing the infrastructure for a widespread vaccination campaign, the need for a delayed two-dose regimen in some jurisdictions to ensure maximum protection,[3] and the delay in the development of antibodies following vaccination. Additionally, as vaccine supply was constrained, most countries opted to prioritise vaccination in high-risk populations, including health-care workers and older people. Such strategies would have generated direct protection but would have had comparatively less impact on SARS-CoV-2 transmission. However, from mid-2021 onwards those countries with access to plentiful vaccine supply opted for mass vaccination of the adult population, later including children and subsequent boosting to maintain high levels of protection given the waning in vaccine efficacy and the emergence of new variants of

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Research in context

Evidence before this study

We searched PubMed up to April 26, 2022, without any date limits or language restrictions, using the search terms "vaccin* AND impact AND (death* OR live*) AND (estimat* OR evaluat*) AND (COVID-19 OR SARS-CoV-2)". We found eight published studies that estimated the impact of COVID-19 vaccination, including deaths averted from vaccination. None of the studies considered the global impact of COVID-19 vaccination, focusing instead on specific regions (Italy, California, North Carolina, Stockholm, subsets of states in the USA, New York City, and the WHO European Region). Furthermore, the study focusing on the WHO European region only quantified the direct impact of vaccination and did not estimate the indirect effects (ie, decreasing infection risk of both vaccinated and unvaccinated susceptible individuals).

Added value of this study

This mathematical modelling study advances previous work both in terms of scale (number of regions modelled) and in terms of quantifying both the direct and indirect impact of COVID-19 vaccination globally. We estimated the impact of vaccination up to Dec 8, 2021, by fitting COVID-19 transmission models to both reported deaths and excess mortality during the pandemic as a proxy for deaths due to COVID-19. This study is, to the best of our knowledge, the first to use excess mortality estimates in this way, allowing for the impact of COVID-19 vaccination to be estimated more accurately in countries with weaker surveillance systems.

Implications of all the available evidence

The results highlight the substantial impact that vaccination has had on the trajectory of the COVID-19 pandemic. They also illustrate the broader impact of COVID-19 vaccination in terms of allowing countries with high vaccine coverage to relax interventions. Furthermore, the findings highlight the importance of equitable access to vaccines, particularly in low-income regions, where substantially more lives could have been saved if the vaccination targets set out by the COVID-19 Vaccines Global Access (COVAX) Facility (20% coverage in COVAX Advance Market Commitment countries by the end of 2021) and WHO (40% coverage in each country by the end of 2021) had been reached.

concern. This approach has resulted in vast inequalities in global vaccine distribution.[4]

To reduce inequality, a fair allocation mechanism for COVID-19 vaccines was developed through the COVID-19 Vaccines Global Access (COVAX) facility, with a key target of achieving 20% vaccine coverage for the countries covered by its Advance Market Commitment (AMC) through COVAX-secured doses by the end of 2021.[5] WHO expanded this target by setting a global strategy to achieve 70% coverage in all countries by mid-2022, with an interim target of 40% coverage by the end of 2021.[5] However, as a result of numerous challenges, particularly the constrained vaccine supply to COVAX (exacerbated by some countries obtaining a greater proportion of the global vaccine supply, pharmaceutical companies not meeting their contractual obligations to COVAX, and unpredictable delays in supply including vaccines with brief expiry windows), these targets were not reached in many lower-middle-income countries and low-income countries.[6] Vaccine uptake has also been suboptimal in many countries because of vaccine hesitancy.[7] This considerable heterogeneity in vaccination coverage has resulted in continued reliance on non-pharmaceutical interventions for pandemic management in some countries[8] but concomitantly enabled other nations to relax interventions as a route out of the pandemic.[9]

Quantifying the impact of vaccination is further challenged by the incomplete picture of the COVID-19 pandemic that is obtained from reported deaths. In many countries, vital registration systems are incomplete and therefore only a fraction of deaths are routinely reported. However, even in countries with complete vital registration systems, it is difficult to accurately define the cause of death in individuals who present with multiple morbidities. Excess all-cause mortality (the difference between the observed and expected number of deaths in non-pandemic years) has therefore been used to quantify the impact of the COVID-19 pandemic.[10] Although the exact contribution of COVID-19 to excess mortality is unknown, the strong temporal correlation observed globally between reported COVID-19 mortality and excess mortality provides evidence that excess mortality is an informative indicator of pandemic-related mortality.[11] Robust vital registration systems do not exist in many parts of the world, with WHO estimating that 40% of global deaths that occurred in 2020 were unregistered,[12] and therefore data on excess mortality are not available for every country. Model-based estimates have therefore been developed to obtain a more complete estimate of the pandemic to date. One set of estimates produced by *The Economist* uses a range of socioeconomic and epidemiological data to infer excess mortality.[13] Although the precise estimates differ between research groups[14] and WHO,[15] they all suggest a substantially larger number of COVID-19 deaths than have been reported to date.

We aimed to quantify the global impact of the first year of COVID-19 vaccination and estimate the number of deaths from COVID-19 averted in 185 countries and territories, both from the direct protection of vaccinated individuals and from the indirect protection of all individuals living in vaccinated environments due to the reduction in risk of infection. Additionally, we aimed to quantify the impact that a more equitable global vaccination campaign, meeting the vaccination targets set by COVAX of 20% vaccination coverage of the eligible population by the end of 2021, could have had in COVAX

AMC countries. We also aimed to quantify the impact of achieving the WHO target of 40% coverage by the end of 2021 in all countries.

Methods

Transmission model fitting

For this mathematical modelling study, we used a previously published COVID-19 transmission model[16,17] and fitting framework[18] to obtain profiles of the COVID-19 pandemic in each country and thus estimate the counterfactual scenario in which vaccines are not delivered. Briefly, the model is a population-based, age-structured susceptible-exposed-infectious-recovered-susceptible (SEIRS) model, which explicitly captures disease severity, passage through different indicated health-care levels, and the roll-out of vaccination. We incorporated country-level data on demography, age-based mixing patterns, and health-care capacity. We fit the model to officially reported COVID-19 deaths in each country, resulting in an inferred time-varying level of transmission, R_t, denoting the mean number of secondary infections in the absence of both infection-induced and vaccine-derived immunity. By fitting directly to mortality, we indirectly captured the impact that non-pharmaceutical interventions have had over the course of the COVID-19 pandemic.

Vaccination rates for first and second doses in each country were taken from Our World in Data[7] and the WHO dashboard. We assumed a vaccination strategy that first targets those most at risk (including health-care workers) and then iteratively distributes vaccines in descending age order. Vaccination was assumed to confer protection against SARS-CoV-2 infection and the development of severe disease requiring hospital admission,[4] and to reduce transmission from vaccine breakthrough infections (ie, we assumed vaccinated individuals who develop infection would be less infectious than unvaccinated individuals).[19] We inferred vaccine efficacy for each country on the basis of vaccine types known to be predominantly used in each country. We explicitly modelled the emergence of the delta (B.1.617.2) variant and its impact on vaccine efficacy, hospital admissions, and immune escape.[20–22] Any epidemiological differences associated with previous variants were assumed to be reflected by their effects on mortality,[23] which were subsequently captured by the estimated R_t trend. We fit the model to COVID-19 mortality in a Bayesian framework using a Metropolis-Hastings Markov Chain Monte Carlo-based sampling scheme. We used the resulting fit to estimate the time-varying reproductive number, R_t, and its associated uncertainty.

Complete details of the model, vaccination, variants, and model fitting are given in the appendix (pp 2–10). No ethical concerns were noted for this study, with all mortality data used based on nationally aggregated statistics; all datasets used were publicly available.

Excess mortality and COVID-19 mortality data

Because of the heterogeneity in death registration and certification worldwide, we also fit the model to all-cause excess mortality. For countries and time periods for which excess mortality had not been reported, we used model-based estimates of all-cause excess mortality, first produced by *The Economist*.[13] More details of the methodology are given in the appendix (p 2). Given the wide uncertainty in these model-based estimates of excess mortality in many parts of the world, we also presented the deaths averted as estimated by fitting to official reported COVID-19 deaths from the Johns Hopkins University COVID-19 Data Repository (appendix p 2). Importantly, these estimates based on official reported COVID-19 deaths represent the lower bound of deaths averted at the global level due to the considerable levels of under-reporting of COVID-19 mortality documented worldwide.[24]

For the **Johns Hopkins University COVID-19 Data Repository** see https://coronavirus.jhu.edu/map.html

Estimating deaths averted due to vaccination

The first vaccination outside a clinical trial setting was given on Dec 8, 2020. We introduced vaccination from this point onwards in the model and explored the impact of the first year of vaccination up to Dec 8, 2021. To quantify the impact of vaccination and its associated uncertainty, we took 100 draws from the estimated distribution of R_t and vaccine efficacy estimates for each country and simulated a counterfactual scenario in which no vaccines are available and the epidemic in each country follows the same R_t trend since the start of the pandemic; a counterfactual in which vaccines are delivered but there are no indirect effects (ie, they do not reduce SARS-CoV-2 transmission); and the observed scenario in which vaccines were delivered at the rates reported. The third scenario generated an estimate of the trajectory of the epidemic for our fitted model and hence closely matched reported COVID-19 or excess deaths or estimated excess deaths in each country. We calculated the deaths averted as a result of vaccination by subtracting the estimated COVID-19 deaths from the simulation with vaccines included (the observed scenario) from the estimated COVID-19 deaths under the first counterfactual scenario. This process is illustrated in the appendix (p 18), which shows the estimated deaths averted for the USA. Because of the difficulty in predicting how governments and populations would have responded, and how viral evolution would have progressed if vaccines had not been available, we made no attempt to adjust the R_t trends for further non-pharmaceutical interventions, changes in mobility, or development of variants that probably would have occurred differently in the absence of vaccination. To explore the impact of key model parameters on estimates of deaths averted, we did additional sensitivity analyses. These included characterising the effects of the assumed relationship between the infection fatality ratio (IFR) and age (appendix p 10), as well as the assumed degree of immune evasion exhibited by the delta variant (appendix p 7).

For the **WHO dashboard** see https://covid19.who.int/

See Online for appendix

	Total COVID-19 deaths	Vaccination coverage (%)	Estimated deaths averted by vaccinations		
			Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	5 469 000 (5 339 000–5 613 000)	38·30%	14 400 000 (13 650 000–15 900 000)	22·81 (21·63–25·18)	25·99 (24·64–28·69)
World Bank income group					
High-income countries	1 956 000 (1 892 000–2 032 000)	68·80%	6 353 000 (6 105 000–6 604 000)	52·6 (50·54–54·67)	36·67 (35·23–38·11)
Upper-middle-income countries	2 287 000 (2 220 000–2 355 000)	50·10%	2 914 000 (2 785 000–3 047 000)	25·6 (24·47–26·77)	23·36 (22·33–24·43)
Lower-middle-income countries	1 188 000 (1 099 000–1 302 000)	29·80%	5 083 000 (4 379 000–6 628 000)	15·27 (13·16–19·91)	20·39 (17·57–26·59)
Low-income countries	36 520 (33 390–40 410)	3·57%	20 380 (17 680–23 870)	0·3188 (0·2766–0·3733)	2·965 (2·572–3·472)
WHO region					
African region	153 800 (145 100–164 700)	5·48%	97 190 (88 420–107 400)	0·8677 (0·7894–0·9589)	5·958 (5·420–6·584)
Region of the Americas	2 492 000 (2 418 000–2 576 000)	58·30%	3 813 000 (3 624 000–3 987 000)	37·46 (35·6–39·17)	29·28 (27·83–30·62)
Eastern Mediterranean region	318 700 (307 200–331 500)	28·10%	639 200 (581 600–707 700)	8·746 (7·958–9·684)	13·50 (12·28–14·95)
European region	1 628 000 (1 589 000–1 673 000)	56·50%	4 334 000 (4 214 000–4 487 000)	46·77 (45·48–48·42)	39·52 (38·43–40·92)
South-East Asian region	713 800 (635 900–807 000)	35·40%	3 913 000 (3 234 000–5 491 000)	19·61 (16·21–27·52)	21·63 (17·88–30·36)
Western Pacific region	149 000 (120 100–234 400)	62·40%	1 574 000 (1 267 000–1 839 000)	30·14 (24·26–35·21)	22·58 (18·18–26·38)

Deaths averted are presented as medians with 95% credible intervals, with values also presented per 10 000 total population and per 10 000 vaccinations (first or second dose). Vaccination coverage is the proportion of the population with a full dose in the modelled countries by Dec 8, 2021. Total deaths are all modelled deaths in the presence of vaccinations when fitted to reported deaths from the start of the pandemic up to Dec 8, 2021.

Table 1: Estimated deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to officially reported COVID-19 deaths

We also explored the impact of increasing vaccine distribution to meet WHO and COVAX targets. We modelled two scenarios in which the targets set by WHO to fully vaccinate 40% of the eligible population in each country and administrative region, and by COVAX to fully vaccinate 20% of the eligible population in AMC countries, by the end of 2021 had been reached. To do so, for countries in which these targets had not been met, we scaled the roll-out of vaccines across the year by a constant factor such that exactly the targeted amount of the population had received their second vaccine dose by our end date (Dec 8, 2021).

Statistical analysis

All analyses were done with R software (version 4.1.3), with all data, code, packages, and versions used available online at GitHub. This analysis covered 185 countries and territories with a population greater than 90 000 as reported in *World Population Prospects 2019*,[25] and that reported at least one death due to COVID-19 or 1 week of positive estimated excess mortality. We excluded China from our estimates because of its unique position as the origin of the detected epidemic and its large influence on estimates of deaths averted stemming from its population size.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Based on our model fit to officially reported COVID-19 deaths, we estimated that 18·1 million (95% credible interval [CrI] 17·4–19·7) deaths due to COVID-19 would have occurred without vaccinations worldwide during the first year of the COVID-19 vaccination programme (Dec 8, 2020, to Dec 8, 2021). Of these, we estimated that vaccination prevented 14·4 million (95% CrI 13·7–15·9) deaths due to COVID-19, representing a global reduction of 79% of deaths (14·4 million of 18·1 million) during the first year of COVID-19 vaccination (table 1). These estimates of vaccine impact do not account for the potential under-ascertainment of deaths related to COVID-19.

Using our model fit to predicted and reported excess mortality (appendix p 23), we estimated that 31·4 million (95% CrI 30·6–32·1) deaths due to COVID-19 would have occurred without vaccinations during the first year of COVID-19 vaccination, with 19·8 million (95% CrI 19·1–20·4) deaths averted, corresponding to 63% (19·8 million of 31·4 million) of total deaths (table 2). The difference between vaccine impact estimates based on excess mortality and official deaths due to COVID-19 was greatest in low-income regions, with approximately ten times more deaths estimated to have been averted in low-income countries when relying on excess mortality estimates (appendix pp 13, 19).

Using our model fit to excess mortality, we estimated that most deaths averted were due to the high levels of individual-level direct protection conferred by vaccination, with 79% (15·5 million of 19·8 million) of deaths averted through direct protection (figure 1A). Vaccine impact was also conferred through reducing the levels of burden placed on health-care systems, reducing the number of days that health-care capacity would have been exceeded and therefore contributing to an overall lower fatality rate from infection (appendix p 20). Throughout 2021, vaccine impact changed over time and space. Vaccine impact was

	Total excess deaths	Estimated deaths averted by vaccinations		
		Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	17 990 000 (17 610 000–18 530 000)	19 810 000 (19 130 000–20 380 000)	31·21 (30·14–32·1)	35·68 (34·47–36·71)
World Bank income group				
High-income countries	2 503 000 (2 412 000–2 609 000)	8 004 000 (7 644 000–8 438 000)	66·18 (63·20–69·77)	46·14 (44·07–48·64)
Upper-middle-income countries	4 717 000 (4 611 000–4 827 000)	4 230 000 (4 051 000–4 384 000)	36·97 (35·40–38·31)	33·71 (32·28–34·94)
Lower-middle-income countries	9 688 000 (9 329 000–10 170 000)	7 401 000 (6 841 000–7 655 000)	22·23 (20·55–23·00)	29·69 (27·44–30·71)
Low-income countries	1 087 000 (1 068 000–1 106 000)	180 300 (171 400–188 900)	2·711 (2·576–2·840)	26·23 (24·93–27·48)
WHO region				
African region	1 614 000 (1 580 000–1 652 000)	466 400 (446 300–487 000)	4·164 (3·985–4·348)	28·59 (27·36–29·85)
Region of the Americas	3 354 000 (3 260 000–3 456 000)	4 469 000 (4 233 000–4 728 000)	43·89 (41·57–46·43)	34·31 (32·50–36·29)
Eastern Mediterranean region	2 310 000 (2 248 000–2 376 000)	992 800 (938 800–1 066 000)	13·58 (12·85–14·59)	20·97 (19·83–22·52)
European region	3 448 000 (3 347 000–3 568 000)	5 811 000 (5 551 000–6 187 000)	62·30 (59·51–66·33)	52·63 (50·28–56·04)
South-East Asian region	6 741 000 (6 398 000–7 247 000)	5 658 000 (5 114 000–5 858 000)	27·99 (25·3–28·98)	31·29 (28·28–32·39)
Western Pacific region	518 700 (489 200–547 800)	2 429 000 (2 266 000–2 617 000)	46·31 (43·21–49·91)	34·74 (32·42–37·44)

Deaths averted are presented as medians with 95% credible intervals, with values also presented per 10 000 total population and per 10 000 vaccinations (first or second dose). Total deaths are all modelled deaths in the presence of vaccinations when fitted to excess mortality from the start of the pandemic up to Dec 8, 2021.

Table 2: Estimated deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to excess mortality

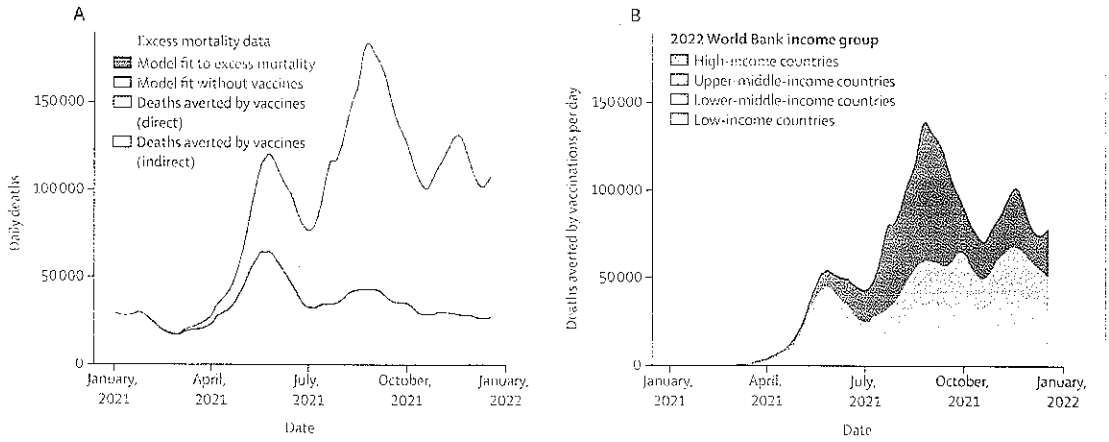

Figure 1: Global COVID-19 deaths averted due to vaccination based on excess mortality

(A) Median number of daily COVID-19 deaths based on excess mortality estimates (grey vertical bars) in the first year of vaccination. The baseline estimate of daily COVID-19 deaths from the model fit to excess mortality is plotted with the solid black line and the counterfactual scenario without vaccines is plotted with a red line. The gap between the red and black line indicates the deaths averted due to vaccination, with the proportion of total deaths averted by direct protection conferred by vaccination shown in blue and indirect protection shown in green. (B) Median number of daily deaths averted per day as per 2022 World Bank income group.

initially concentrated in lower-middle-income countries (figure 1B), resulting from the significant epidemic wave in India as the delta variant emerged. This was subsequently followed by vaccine impact being concentrated in high-income countries that were then either able to relax interventions due to high vaccination coverage (eg, the UK), or that did not implement further restrictions despite the spread of the more virulent delta variant in the second half of 2021.

Overall, estimated deaths averted per capita were highest in high-income countries, reflecting the earlier and wider roll-out of vaccination campaigns (table 2, figure 2; appendix p 13). We estimated that substantially more deaths were averted in the WHO European region. This was due to both the greater number of vaccinations administered in these regions and the higher levels of vaccine coverage achieved before the arrival of the delta variant.

The estimated number of deaths averted per vaccine administered was notably higher in high-income countries and upper-middle-income countries, in part due to greater access to the more efficacious mRNA vaccines (table 2;

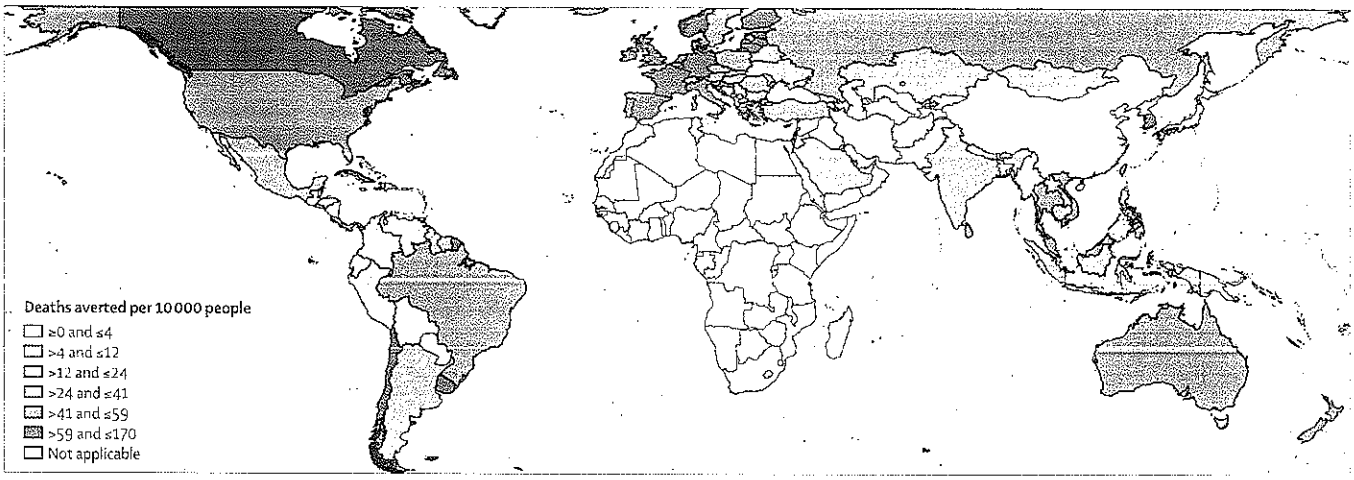

Figure 2: Median deaths averted by vaccinations per 10 000 people by country in the first year of COVID-19 vaccination
Estimates of deaths averted were based on model fits to excess mortality and were binned within seven equal quantiles starting at 0 deaths averted. Deaths averted listed as not applicable for China because of its exclusion from our analysis, due to its unique position as the origin of the detected epidemic and large influence on estimates of deaths averted stemming from its population size.

appendix p 14). Across the geographical regions, the estimated number of deaths averted per vaccine administered was estimated to be significantly higher in the European region and significantly lower in the Eastern Mediterranean region, reflecting disparities in access to different vaccine types (appendix p 14) coupled with very high predicted excess mortality in several countries in the Eastern Mediterranean region (table 2). The disparity in the number of deaths averted per vaccine between the European region and the Western Pacific region, despite access to similar vaccine types, reflects the zero-COVID strategy adopted by some countries in the Western Pacific region, such as New Zealand, which resulted in smaller epidemics predicted in the no-vaccine counterfactual (table 2; appendix p 13). Conversely, we estimated the greatest vaccine impact to have occurred in high-income countries that did not pursue a zero-COVID strategy (appendix p 13), reflecting how maximising vaccination coverage was leveraged to re-open the economy, resulting in increased transmission and subsequently higher inferred R_t trends. When viewed across income strata, a linear log–log relationship was observed between per-capita deaths averted and vaccines administered (figure 3), with low-income countries estimated to have a lower vaccine impact resulting from lower vaccine coverage. This relationship was weakest within high-income countries, as all high-income countries had high levels of vaccinations per capita, with the variation in deaths averted explained by other heterogeneities in their epidemics, such as pursuing zero-COVID strategies.

For the 83 COVAX AMC countries modelled, using our model fit to excess mortality, we estimated that 17·9 million (95% CrI 17·2–18·5) deaths due to COVID-19 would have occurred without vaccinations during the first year of COVID-19 vaccination. We estimated that vaccinations averted 7·4 million (95% CrI 6·8–7·7) deaths, 41% (7·4 million of 17·9 million) of the deaths that would have occurred in COVAX AMC countries. Notably, the shortfall of the COVAX target in several regions was estimated to have resulted in an additional 156 900 (95% CrI 147 800–165 400) deaths (table 3). Although these deaths constituted a small proportion of the total deaths averted globally, these avertable deaths were concentrated in 25 low-income countries, which we predict would have averted an additional 81 750 (95% CrI 75 430–88 200) deaths across low-income countries by reaching 20% coverage, representing an additional 45% of deaths averted (table 3).

We found that 96 countries and administrative regions were below the WHO target of 40% vaccination coverage by the end of 2021. Had this target been met, we estimated that 599 300 (95% CrI 577 700–622 400) additional deaths would have been averted (table 3). The majority of these deaths occurred in lower-middle-income countries and the African and Eastern Mediterranean regions, although the largest proportional increase was seen in low-income countries, with the averted deaths making up a 111% increase in estimated deaths averted by vaccinations (table 3).

Our vaccine impact estimates were dependent on the assumed level of immune escape shown by the delta variant and the assumed relationship between age and the IFR. In the scenario in which the epidemic wave caused by the delta variant was comparable to previous waves and neither reached herd immunity nor resulted in health-system capacity being breached, our estimates of vaccine impact were unchanged regardless of the assumed level of immune evasion associated with the delta variant (appendix p 21). However, in scenarios in which the introduction of the delta variant produced a significantly larger wave that resulted in herd immunity being reached in the counterfactual, increased immune escape associated with the delta variant resulted in an

increased number of averted deaths due to the larger effective size of the susceptible population. In sensitivity analyses in which the relationship between age and IFR was changed, we estimated that vaccine impact would be greater in scenarios with higher IFRs, reflecting the higher number of deaths that could be averted by vaccination (appendix p 22).

Discussion

The high individual-level protection against severe disease and mortality due to COVID-19, as well as the population-level benefit afforded by mild protection against SARS-CoV-2 infection (before the emergence of the omicron [B.1.1.529] variant), conferred by vaccination, has fundamentally altered the course of the COVID-19 pandemic. Directly measuring the impact of vaccination programmes on COVID-19 mortality is not possible as the counterfactual (ie, without vaccinations) cannot be observed. Mathematical models are a valuable tool for quantifying the impact of vaccination campaigns on epidemic dynamics.[15] We evaluated the impact of the first year of COVID-19 vaccination, revealing how vaccinations have more than halved the potential global death toll due to COVID-19, with an estimated 19·8 million deaths from COVID-19 averted as a result of vaccination, based on excess mortality estimates of the impact of the pandemic. These reductions were concentrated in high-income countries that relied on their vaccination programmes to relax interventions and allow SARS-CoV-2 transmission to increase as they moved into a new stage of the pandemic.

In low-income countries, particularly countries that did not reach the 20% targets set out by COVAX, vaccine impact was substantially lower, with vaccine impact estimated to have been almost doubled if the targets had been reached. If the 40% target, per country, from WHO had been met, we estimated a further increase in deaths averted, mainly focused in lower-middle-income countries and low-income countries. A limitation of our assessment of the COVAX and WHO targets is the timeframe of our analysis, as these targets were set to be reached by the end of 2021, whereas our modelling endpoint was Dec 8, 2021, to align with 1 year since the start of public vaccination. Hence, some countries might have moved closer to achieving the targets, or achieved them, by the end of the year. However, any recent vaccination drives would have had consequently negligible impact given the delay in developing protection and insufficient impact on COVID-19 dynamics.

Deriving estimates of vaccine impact is heavily dependent on the counterfactual scenario chosen. In our counterfactual, we assumed the same time-varying levels of SARS-CoV-2 transmission as estimated in our model fits. Consequently, the largest impact was observed in countries that delivered the most vaccinations to date and simultaneously relaxed interventions, allowing SARS-CoV-2 transmission to increase. However, several countries with slower vaccination roll-out as well as countries adopting a zero-COVID strategy maintained stronger interventions to suppress transmission and thus observed smaller impacts of their vaccination programmes as a result. As these countries start to reopen, we predict that vaccine impact estimates would increase in line with increasing levels of SARS-CoV-2 transmission.

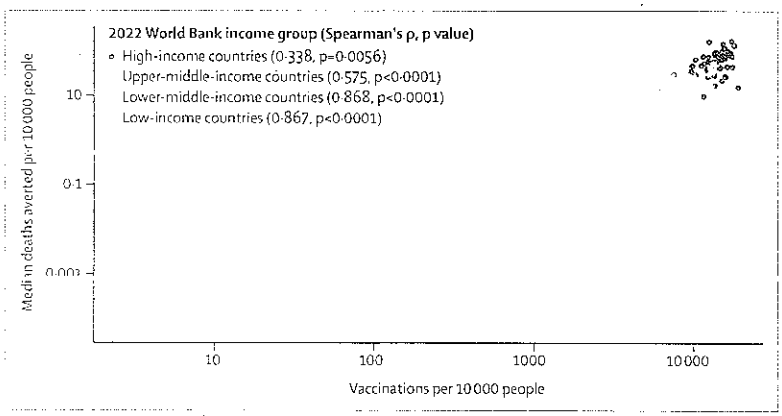

Figure 3: **Median deaths averted by vaccinations per 10 000 against vaccinations per 10 000 for each country**
All measures are on the log-scale. Spearman's rank correlation coefficient (Spearman's ρ) is also given for each income group with a p value based on the Z score against a null hypothesis of no correlation. Countries that did not deliver any vaccinations or had no deaths averted are not included.

Under-ascertainment of COVID-19 mortality is a known issue that has hindered our understanding of the pandemic.[15] In this analysis, we consequently focused on fitting to all-cause excess mortality, which provides a more complete description of the pandemic.[15] However, even when relying on model fits based on reported COVID-19 deaths, we estimated that more than 14 million deaths were averted by COVID-19 vaccination. The discrepancy between vaccine impact estimates based on excess mortality and COVID-19 deaths was concentrated in settings with lower death registration and certification. This substantial discrepancy underpins the crucial need for continued investment in civil registration and vital statistics to prevent biases in mortality reporting further minimising the perceived impact and necessity of vaccination in settings with lower reporting of deaths. In countries with more complete reporting systems, our estimates were broadly comparable to other endeavours focused on officially reported COVID-19 deaths and on understanding the direct impact of vaccination on people older than 60 years in Europe.[36] We identified one study that estimated both the indirect and direct impact of vaccination, which again yielded estimates for vaccine impact in the USA that were similar to our impact estimates based on reported COVID-19 deaths.[37]

In our effort to provide impact estimates globally, we introduced various assumptions into our model. We were hindered by the global disparities in SARS-CoV-2 genomic surveillance and the absence of detailed vaccination data for the majority of countries. Consequently, key model

	COVAX target (20% of eligible population in COVAX Advance Market Commitment countries fully dosed)				WHO target (40% of eligible population fully dosed)			
	Countries failing target	Increased vaccine coverage (%)	Additional deaths averted	Additional deaths averted* (%)	Countries failing target	Increased vaccine coverage (%)	Additional deaths averted	Additional deaths averted* (%)
Worldwide	41	4·15%	156 900 (147 800–165 400)	0·792% (0·744–0·843)	96	27·8%	599 300 (577 700–622 400)	3·03% (2·89–3·17)
World Bank income group								
High-income countries	..	..	..	..	1	0·00191%	20 (20–30)	0·000298% (0·000243–0·000342)
Upper-middle-income countries	..	..	..	..	27	6·1%	51 110 (47 860–66 690)	1·21% (1·12–1·58)
Lower-middle-income countries	16	4·28%	75 540 (68 640–80 380)	1·02% (0·923–1·13)	41	39·7%	347 500 (330 300–363 300)	4·71% (4·43–5·11)
Low-income countries	25	253%	81 750 (75 430–88 200)	45·2% (42·0–49·3)	27	1060%	200 000 (187 900–211 900)	111% (105–118)
WHO region								
African region	31	134%	132 700 (123 800–141 300)	28·4% (26·5–30·4)	44	631%	348 900 (330 200–370 000)	74·9% (70·7–78·8)
Region of the Americas	1	0·248%	1080 (850–1390)	0·0241% (0·0186–0·0308)	14	1·66%	6330 (5870–6840)	0·141% (0·129–0·155)
Eastern Mediterranean region	6	5·56%	20 850 (18 860–22 710)	2·09% (1·86–2·32)	13	61·6%	126 800 (118 900–134 600)	12·7% (11·6–13·7)
European region	..	..	..	..	13	3·05%	41 760 (38 110–46 160)	0·715% (0·644–0·799)
South-East Asian region	1	0·586%	1410 (50–2960)	0·0254% (0·000914–0·0532)	7	17·5%	70 420 (64 300–75 890)	1·25% (1·15–1·39)
African region	2	0·302%	900 (610–1200)	0·0366% (0·0250–0·0492)	5	2·59%	4990 (4390–5730)	0·205% (0·178–0·237)

Data are n (95% credible interval [CrI]) or % (95% CrI). All percentages are reported to 3 significant figures. Increased vaccination coverage is defined as the percentage increase in the proportion of the population with a full dose in all modelled countries when meeting the respective targets. Countries are grouped by 2022 World Bank income group and WHO region. COVAX=COVID-19 Vaccines Global Access.
*In proportion to total deaths averted by vaccines, as shown in table 2.

Table 3: **Estimated increase in deaths averted in the first year of COVID-19 vaccinations worldwide based on fits to excess mortality had all countries met either of the COVAX or WHO vaccination targets**

inputs had to be created from working assumptions on which vaccines were delivered, how they were delivered, and when new variants of concern spread worldwide. We also assumed that the relationship between age and IFR was the same for each country. These assumptions would have affected our estimates of deaths averted, with sensitivity analyses showing that higher overall IFRs will increase the number of deaths that could be averted by vaccination. Our impact estimates were also limited by the inherent uncertainty in model-based estimates of excess mortality.[13] These estimates are likely to have underestimated or overestimated COVID-19 death tolls in many countries. Notably, our model fits were unable to recreate excess mortality death tolls in recent epidemic waves in Iraq and Sudan because of the depletion of the susceptible population. These discrepancies could have been due to multiple reasons, including overestimated excess mortality, proportions of excess mortality not due to COVID-19,[28] higher infection fatality rates by age in low-income settings than those estimated from high-income countries,[29] and lower vaccine effectiveness than assumed in our framework. Last, our impact estimates were dependent on the assumed degree of immune escape that each variant of concern exhibits.[29] If immune escape was higher than we assumed, more of the population would have been susceptible to re-infection and consequently more deaths from COVID-19 could have been averted by vaccination.

More broadly, our estimates should be considered in light of the considerable uncertainty inherent in estimating vaccine impact. Uncertainty in the true death toll of the pandemic, the circulating variants of concern and their immunological phenotypes, and the vaccines themselves administered in many countries vastly complicate efforts to derive accurate estimates of the impact of COVID-19 vaccines. However, the results of this analysis still provide a comprehensive and thorough assessment of the impact of COVID-19 vaccination, revealing the substantial impact that vaccines have had and the millions of lives that are likely to have been saved during the first year of vaccination. Despite this, more lives could have been saved if vaccines had been distributed more rapidly to many parts of the world and if vaccine uptake could have been strengthened worldwide. Reaching vaccination coverage targets and improving vaccine coverage globally is dependent on multiple factors and not solely dependent on improving

vaccine donations.[9] Vaccine intellectual property needs to be shared more quickly in the future, with more open technology and knowledge transfer surrounding vaccine production and allocation. Vaccine distribution and delivery infrastructure also needs to be scaled up worldwide and misinformation combatted to improve vaccine demand. Improvements must be made in all these areas to reach current vaccine targets and help ensure that vaccines are more equitably distributed in the future.

Contributors

OJW and ACG conceived the study with input from GB, ABH, PW, and JT. OJW and GB led the model fitting and counterfactual simulation analyses for the estimation of deaths averted. OJW and GB produced the first draft of the manuscript and have accessed and verified the underlying data. All authors read, contributed to, and approved the final draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ACG has received personal consultancy fees from HSBC, GlaxoSmithKline, and WHO related to COVID-19 epidemiology and from The Global Fund to Fight AIDS, Tuberculosis and Malaria for work unrelated to COVID-19. ACG is a non-remunerated member of scientific advisory boards for Moderna and the Coalition for Epidemic Preparedness. ABH and PW have received personal consultancy related to COVID-19 work from WHO. All other authors declare no competing interests.

Data sharing

All data, codes, and supplementary tables used and generated by this study are available in a GitHub repository (version 1.0.1) or the Zenodo open repository. All estimates of deaths averted from vaccination are available in the appendix (p 13).

Acknowledgments

This work was supported by a Schmidt Science Fellowship in partnership with the Rhodes Trust (OJW), Centre funding from the UK Medical Research Council (all authors), grant funding from WHO (OJW, ABH, PW, and ACG), Gavi, The Vaccine Alliance, and the Bill & Melinda Gates Foundation (JT and ACG), support from the Imperial College Research Fellowship (PW and ABH), and support from the National Institute for Health Research Health Protection Research Unit in Modelling Methodology and Community Jameel (all authors). We thank Sondre Ulvund Solstad from *The Economist* for developing excess mortality statistics and their help in interpreting these estimates.

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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;

(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.

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.

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.

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;

(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

(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,—

(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

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.

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;

(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

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.

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.

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:

(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.

(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.

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.

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.

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 paramieters			
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

* 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).

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.

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

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.

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

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.

(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.

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: _____/ ____ /

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.

(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.

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/incidences 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

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

(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

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.

(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

(*See 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.

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.

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)

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:.....

Date:.....

Digital Signature

(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-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:.....

Date:.....

Digital Signature

(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]	

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:.....

Date:.....

Digital Signature

(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: .....

Date: .....

Central Licencing Authority

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: .....

Date: .....

Central Licencing Authority

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____.	

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)

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:

Date:

Digital Signature

(Name and designation)

Annexure:

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:.....

Date: .....

Central Licencing Authority

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.

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:

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 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)

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: .....

Date: .....

Central Licencing Authority

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:

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:	
Manufacturer of the raw material (active pharmaceutical ingredient):	

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-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: .....

Date: .....

Central Licencing Authority

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: .....

Date: .....

Central Licencing Authority

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.	

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------.

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:

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:.....

Date: .....

Digital Signature

(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.

Place.....

Date.....

Signature

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: .....

Date: .....

Central Licencing Authority

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.	

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:.....

Date: .....

Digital Signature

(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.....

Date.....

Signature

Medical Superintendent of the Government Hospital or Head of Medical Institution

[Stamp]

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: .....

Date: .....

Central Licencing Authority and Stamp

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	

* **Write NA where not applicable.**

[F.No.X.11014/10/2017- DRS -Part (1)]

Dr. MANDEEP K. BHANDARI, Jt. Secy.

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Uploaded by Dte. of Printing at Government of India Press, Ring Road, Mayapuri, New Delhi-110064
and Published by the Controller of Publications, Delhi-110054.

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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

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several years.

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Chronology of Events ChAdOx1 nCoV-19 [COVISHIELD] manufactured by M/s Serum Institute of India Pvt. Ltd., Pune (above 18 years age)

Date	Event Description	Remarks
-03 May 2020	M/s Serum has submitted application in CT-10 for grant of permission to manufacture ChAdOx1 nCoV-19 Corona Virus Vaccine for examination, Test & Analysis purpose.	
03 May 2020	CDSCO has granted permission in CT-11 for manufacture of ChAdOx1 nCoV-19 Corona Virus Vaccine for examination, Test & Analysis purpose.	
24 July 2020	M/s Serum has submitted an application in Form CT-04 for grant of Permission in Form-CT-06 to conduct Phase II/III clinical trial for ChAdOx1 nCoV-19 Vaccine [COVISHIELD].	Application Form CT-04
28 July & 31 July 2020	The application to conduct Phase II/III clinical trial for ChAdOx1 nCoV-19 Vaccine was deliberated by the Subject Expert Committee (SEC)	
01 Aug 2020	Serum has submitted application in CT-10 for grant of permission to manufacture/ use of ChAdOx1 nCoV-19 Corona Virus Vaccine for clinical trial purpose.	
02 Aug 2020	CDSCO granted permission to conduct Phase II / III Clinical Trial of ICMR/SII-COVISHIELD vaccine on 02 Aug 2020 vide CT No.: CT-18/2020	02 Aug 2020
05 Aug 2020	CDSCO has granted permission in CT-11 for manufacture/use of ChAdOx1 nCoV-19 Corona Virus Vaccine for clinical trial purpose.	
10th September 2020	SIIPL Response to CDSCO Letter No. BIO/CT/20/000095 dated 09 Sep 2020 w.r.t safety concerns	
15th September 2020	SIIPL Letter of Permission to restart enrolment in Phase II/III study of Covishield in response to DCGI Let BIO/CT/20/000095 dated 11 Sep 2020.	
06th October 2020	Request by SIIPL for approval of amended Protocol Version 3.0 dated 06 Oct 2020	DCGI Dy No 7617 dated 07 Oct 2020
14th October 2020	Request by SIIPL for approval of amended Protocol Version 4.0 dated 14 Oct 2020	DCGI Dy No 7898 dated 15 Oct 2020
16th October 2020	CDSCO Approval vide Letter No. BIO/CT/20/000095 dated 16 Oct 2020 of amended Protocol No. ICMR/SII-COVISHIELD Version 4.0 dated 14 Oct 2020.	
02nd December 2020	DSMB comments on SAEs and DSMB Chair Recommendation submission.	
06th December 2020	Application for Emergency Use Authorization Application	
09 December 2020	The application for the grant of permission to manufacture Covishield was deliberated by the SEC	
30 December 2020 & 01 January 2021	The application for the grant of permission to manufacture Covishield was further deliberated by the SEC	
03rd January 2021	CDSCO has granted permission to manufacture ChAdOx1 nCoV-19 Corona Virus Vaccine for Restricted Use in Emergency situation (MF/BIO/21/000001) subject to certain conditions.	

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Chronology of Events ChAdOx1 nCoV-19 [COVISHIELD] manufactured by M/s Serum Institute of India Pvt. Ltd., Pune (above 18 years age)

Date	Event Description	Remarks
25th October 2021	SIIPL submitted application for omitting the condition Restricted Use in Emergency situation in the permission to manufacture ChAdOx1 nCoV-19 Corona Virus Vaccine.	
14.01.2022 & 19.01.2022	The proposal for omission of the condition Restricted Use in Emergency situation was deliberated by the SEC.	203rd & 204th meetings held on 14.01.2022 & 19.01.2021
27.01.2022	CDSCO omitted the condition restricted use in emergency situation in the permission to manufacture ChAdOx1 nCoV-19 Corona Virus Vaccine for sale or for distribution under New Drugs and Clinical Trials (NDCT) Rules, 2019 in adult population	

05.03.2021 onwards: AEFI Secretariat, MoHFW has frequently forwarded cumulative line list of severe/serious AEFIs reported following use of COVID-19 vaccinations containing vaccine batch details, number of vaccine doses, type of adverse event, date of vaccination & onset of AE etc. along with causality assessment results of AEFI'S that are approved by national AEFI committee through email.

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CODE OF PRACTICE

JULY 2015

Proposed review date: December 2019

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23/11/21

CODE OF PRACTICE

NATIONAL TECHNICAL ADVISORY GROUP ON IMMUNISATION

Introduction

1. The National Technical Advisory Group on Immunisation (NTAGI) was established by an order of the Ministry of Health and Family Welfare (MoHFW) in 2001. As India's apex advisory body on immunization, the NTAGI provides guidance and advice to the MoHFW on **provision of vaccination and immunization services for the effective control of vaccine preventable diseases in the country**.
2. Since its establishment, the NTAGI has been reconstituted twice, in 2010 and 2013. As per the MoHFW order dated 25 June 2013 (13011/01/2013), the NTAGI now includes a Standing Technical Sub-Committee (STSC). The STSC is tasked with undertaking technical review of scientific evidence on matters related to immunization policy and programmes. Final recommendations are drafted by the NTAGI taking into account the scientific review by the STSC and any other relevant evidence.
3. This Code of Practice contains information about the responsibilities, structure, functioning, and procedures of the NTAGI and STSC. This document has been prepared after reviewing the best practices at global and national scientific advisory committees and has been ratified by chair & co-chairs of the NTAGI with inputs from members of the STSC. All members (current and prospective) of the NTAGI and STSC as well as individuals attending meetings are required to confirm their acceptance of the provisions set out in this document by signing the declaration as indicated [Annexure 1].
4. The Code of Practice must be reviewed every five years. An earlier review of the Code of Practice may be taken up, if needed, at the discretion of Chair and Co-chairs.

Objective and scope of activities

5. The overall objective of the NTAGI is to provide advice to the Ministry of Health and Family Welfare on the strategies to control the burden and appropriately evaluate the impact of immunization on Vaccine Preventable Diseases (VPDs) in the country.

6. The NTAGI shall evaluate licensed vaccines as well as prioritize other related interventions such as associated immune globulins and chemo-prophylactic agents and new technologies for delivery, logistics, disease prevention and monitoring of VPD prevalence, vaccination programme and other adjuncts to VPD control'. Guidance for use of unlicensed vaccines may be developed if circumstances necessitate their use.

7. NTAGI recommendations may include guidance on all matters related to immunization policy and programmes:

   - route, dose and frequency of administration of the vaccine
   - population groups (e.g. high risk groups, urban slums and tribal populations)
   - circumstances (e.g. pandemics, natural disaster etc.) in which a vaccine or related agent is recommended
   - strategies for introduction of the vaccine (e.g. pilot/phased introduction, Special Immunization Activities (SIAs), vaccines for post-exposure prophylaxis etc.)
   - contraindications and adverse events associated with the vaccine or related agent
   - recommendations on generation of relevant evidence, prior to and after vaccine introduction, monitoring of delivery and impact after vaccine introduction.

8. In developing these recommendations, the NTAGI may consider (all available, including domestic evidence, wherever available") evidence on burden and epidemiology of disease, vaccine safety, efficacy and effectiveness, economic analyses and implementation issues. In the

absence of available evidence, the NTAGI may also recommend to the government the requirement for specific studies or cumulation of data. The NTAGI may revise or withdraw their recommendation(s) regarding a particular vaccine in the light of new information on any of the criteria mentioned above.

9. The NTAGI may also recommend relevant studies to be conducted (pilot/operational) for vaccines e.g. Post marketing surveillance study for a vaccine may be recommended to the national regulatory authority, technological assessments of new vaccine delivery technologies and studies for impact assessment of new vaccine introductions may be recommended, if and when required.

10. The NTAGI also may provide recommendations that address the general use of vaccines and immune globulin preparations, including travel vaccinations or occupational health vaccinations. These general recommendations may address the principles that govern administration technique; dose and dosing interval; recognized contraindications and precautions; profile of adverse events; the correct storage, handling, and recording of vaccine and immune globulin preparations; and immunization in special situations (e.g. pandemics or natural disasters) or special populations (e.g. urban slums, tribal populations, adolescents, school or college students vaccinations at work etc.) that may warrant new recommendations or modification of the routine recommendations.

11. The NTAGI shall also establish and appropriately revise, a list of vaccines for administration to children and adolescents, adults, pregnant women and immunocompromised individuals eligible to receive vaccines through the Universal Immunization Programme (UIP), along with schedules regarding the appropriate dose and dosing interval, and contraindications to administration of the vaccines.

12. The NTAGI must review its recommendation on every major VPD at least once every five years.

Recommendations formulated by the NTAGI shall be used by the Government to inform, develop and make policy relevant to immunization. **The NTAGI is not a policy making body in its own right and has no regulatory function.** Membership and composition of the NTAGI

Membership

13. The NTAGI is chaired by the Secretary of Health and Family Welfare (H & FW), Ministry of Health and Family Welfare, while the Secretary of Department of Biotechnology, Ministry of Science and Technology and the Secretary of Department of Health Research, Ministry of Health and Family Welfare serve as the Co-chairs, all functioning in an ex-officio capacity.
14. Core membership is composed of Government of India representatives functioning in an ex-officio capacity and independent experts. Core independent experts are expected to serve in their own personal capacity and to not represent the interest of any particular group or organization. In addition, liaison members comprised of representatives of MoHFW, professional organizations and international partners functioning in an ex-officio capacity, as notified in the NTAGI reconstitution order, represent their respective organizations.
15. The Chair, Co-chairs and independent Core Members engage in advising and deciding on final recommendations.
16. Liaison members and ex-officio members (other than the Chair and Co-Chair) may contribute to the discussion, but are not engaged in decisions or final recommendations.
17. Ex- officio members and liaison representatives are expected to represent the position and views of their organizations/departments. Members can only serve in one capacity.

18. As per reconstitution order dated 25 June 2013, Members of the NTAGI will not be paid an honorarium but the costs of their travel and incidentals will be covered for participating in meetings and discussions.

Appointment of NTAGI members

19. NTAGI members are selected based on their expertise and qualifications necessary to contribute to the accomplishments of the NTAGI's objectives. The membership of NTAGI will normally include one to two experts from the following disciplines: epidemiology, biotechnology, infectious diseases, community medicine, pharmacology, vaccinology, health economics, paediatrics, virology, bacteriology, immunology, neurology, mathematical modelling, general practice, public health, nursing, clinical research, community engagement and communication or other relevant disciplines, health systems and delivery and management of immunisation programmes.

20. Distinguished experts in relevant fields will be nominated and appointed as Core Independent Members of the NTAGI and its Sub-committee(s) by the NTAGI chair, the Secretary of Health and Family Welfare, in consultation with the Co-chairs, the Secretary of Biotechnology and the Secretary of Health Research. Experts will be evaluated on the following key attributes for nomination to the NTAGI:

- An outstanding record of achievement and professional and personal credibility in their field of work;
- Advanced training and scientific knowledge of vaccines, immunization and immunization programs;
- Expertise and strategic experience of working in high level advisory roles;
- A deep understanding, expertise and experience in the field of immunization related areas covered by NTAGI;
- An understanding of national immunization issues in the Indian context;

- Excellent interpersonal and communication skills to support effective discussion with a range of stakeholders;
- Ability to evaluate complex issues and weigh conflicting opinions;
- Ability to influence at a senior level;
- A broad range of expertise and interest in vaccines and immunization

21. New members of NTAGI will undergo one day of orientation which will be arranged by the Secretariat, prior to attending a meeting of the NTAGI or its STSC. The new members will review the structure and function of the Indian public health immunization system, the functioning of global and regional technical advisory groups on immunization. They will be introduced to the functioning of the Secretariat for the NTAGI. They will be provided with a briefing that covers the roles and responsibilities of the NTAGI and its membership, the function, operation and practices of NTAGI and its working groups, the support that the secretariat provides, the type of evidence reviewed by NTAGI, the methods for review and how the NTAGI interacts with its stakeholders and all the various aspects covered in this Code of Practice.

22. All core independent members of NTAGI will serve a three-year term, and will be eligible for renewal once, after which they will be rotated off the NTAGI. At a minimum, each member will serve a three-year term with up to one third of members rotating off each year in order to ensure continuity. Renewals of appointments are at the discretion of the Chairs and Co-chairs.
23. A core independent member who has served their maximum term, a total of six years including extension can be reappointed after an absence from the group of one term (three years).
24. Liaison members can continue to serve as long as they continue to hold the posts represented on the NTAGI.

Termination

25. Membership of an individual may be terminated by the Chair in consultation with the Co-chair in the following scenarios:

A) Failure to attend three consecutive unchanged scheduled meetings without prior notification or subsequent explanation

B) Change in affiliation, resulting in a conflict of interests

C) Breach of the confidentiality agreement

Standing Technical Sub-Committee

26. The Standing Technical Sub-Committee (STSC) is tasked with reviewing data and deliberating on specific technical issues, which may require more detailed consideration than would be possible by the NTAGI and that may need substantial input from additional experts who are not NTAGI members. Members of the STSC are members of and will also be involved in the decision making process at the NTAGI.

27. The STSC is co-chaired by the Secretary, Department of Health Research (DHR) and Secretary, Department of Biotechnology (DBT).

28. Members of the STSC (excluding ex-officio members) will comprise of ten to fifteen independent experts appointed by the Secretary (H & FW) in consultation with the Secretary, DBT and Secretary DHR. Members may include experts relevant fields such as epidemiology, biotechnology, infectious diseases, community medicine, pharmacology, vaccinology, health economics, paediatrics, virology, and others which are covered in para 19. Ex-officio members of the STSC will include Director (Epidemiology and Communicable Diseases), ICMR, two state immunization officials by rotation across states for one term each and one Director of an institution that conducts vaccine preventable disease surveillance (e.g. Director National Centre for Disease Control or Director, National Vector Borne Disease Control Programme).

29. Representatives of vaccine manufacturers may not serve as members of STSC, but at the discretion of the co-chairs may be invited to make presentations and answer questions for informing the discussion at hand, especially regarding forecasting trends for preparedness, scientific advances in industry etc. Following presentations all non-STSC members may be asked to leave in order to allow deliberations to be limited to members of the STSC.

30. Confidential or proprietary information received by the STSC may be discussed at STSC meetings since all STSC members and meeting participants will have fulfilled confidentiality and conflict of interest requirements. Meeting participants and members are individually responsible for maintaining confidentiality where such information has been presented or discussed. All STSC findings and recommendations will be presented to the NTAGI where these can be further deliberated. Confidential and proprietary information may be discussed with NTAGI members in closed sessions.

31. Unless otherwise mentioned, the responsibilities of the STSC members and the functioning of the STSC will follow the same guidelines as the NTAGI, outlined in this document.

32. In order to facilitate its functioning, the STSC will establish working groups of two types, standing and ad-hoc, both of which will be supported by the NTAGI secretariat. The standing working groups will have at least two STSC members with one acting as chairperson, other expert members of the standing working group will be nominated by the STSC and approved by the co-Chairs. Ad-hoc groups will be established when needed by direction of the co-Chairs and will include two STSC members and external subject experts who will be co-opted by consensus of the co-Chairs and all STSC members. The working groups will meet as often as required, in order to fulfil objectives defined below.

33. The standing working groups will work on i) Vaccine preventable disease surveillance and ii) Research and capacity building for the functioning of the NTAGI. The standing working groups

will prepare an annual work plan and report to the NTAGI STSC on progress at least annually. The Secretariat will be responsible for organization of meetings, liaising with stakeholders, obtaining relevant data and publications and supporting the working group for synthesis and presentation to the STSC and NTAGI.

34. The ad-hoc working groups will be constituted as time-limited groups to address specific issues. The group will define its terms of reference at its first meeting and circulate them, prior to initiation of activities. When considering a topic (e.g. a new vaccine for introduction in the UIP), the working group will hold meetings, call on relevant experts for discussions, review available data and literature and synthesize the information for presentation to the STSC. They will be supported in these efforts by the Secretariat who will be responsible for organization of meetings, liaising with stakeholders, obtaining relevant data and publications and supporting the working group for synthesis and presentation to the STSC and NTAGI.

Secretariat

35. The NTAGI Secretariat will be financially supported by Government of India.
36. The Secretariat will provide necessary support for organization of meetings of NTAGI and STSC and other associated activities. However, the secretariat does not play a role in setting of agenda, decision making process and functioning of NTAGI.
37. In consultation with the relevant STSC working group, the NTAGI Secretariat will prepare materials in advance of each meeting, which will be circulated to members at least two weeks prior to each meeting. The Secretariat will consult with the working groups and Chairs to invite relevant external topic experts to present at NTAGI and STSC in person or through web links.
38. The NTAGI Secretariat support staff will attend meetings in order to facilitate and to record minutes. These staff will remain throughout the discussion and approval of recommendations, but will not participate in the discussion, recommendations, or voting.

Standard operating procedures for meetings

Calendar and Frequency of meetings

39. The meeting dates for the NTAGI and STSC are to be determined and circulated one year in advance to members by the Secretariat in consultation with the NTAGI Chair and Co-chairs. Box 1 below describes the Standard Operating Procedures for meetings.
40. The NTAGI will meet at least once a year or more frequently, if required. The STSC will meet at least every three months or more frequently, if required.
41. Under exceptional circumstances, a meeting may be called which was not scheduled on the calendar and without the usual two weeks for preparation.
42. Unless there are exceptional circumstances, scheduled meetings may not be cancelled or rescheduled and in such situations, the meeting should be rescheduled at the next available date.

Agenda preparation

43. The agenda for the STSC will consist of i) standing items that will be reviewed at least annually with at least one item reviewed at each STSC meeting and ii) new topics identified for discussion by stakeholders.
44. Standing items for annual STSC review include i) report on routine immunization/surveys, ii) report on any special initiatives on/innovations related to immunization, iii) report of vaccine preventable disease surveillance programmes, iv) report from the National AEFI Committee, v) recommendations from global and regional advisory committees on immunization (e.g. SAGE minutes, WHO position papers) and vi) reports on any impact assessment or special studies related to immunization. Standing items may be included or deleted from the list by consensus of the STSC and co-Chairs.

45. New topics for consideration by the NTAGI and STSC may be identified by the Chair, Co-chairs, members of the STSC and health professionals from the community. The agenda for each meeting will be prioritized taking into account the public health need/urgency, as requested by the MoHFW through the Deputy Commissioner, Immunization, MoHFW.

46. The proposed list of items for review at future meetings of the STSC or NTAGI will be maintained by the Secretariat and will be reviewed once a year at a STSC meeting, when the schedule of meeting dates for the following year is drawn up. Based on recommendation of the Chair and Co-chairs, the Secretariat in consultation with MoHFW will prepare and circulate an agenda at least two weeks before each meeting of the NTAGI or the STSC to allow for members to prepare for the discussion.

47. Secretariat staff will further consult with the working groups, Chair and Co-chairs to arrange for relevant outside experts to present to the NTAGI and STSC.

48. The NTAGI will review every major vaccine preventable disease at least once every five years to evaluate if revised recommendations are necessary.

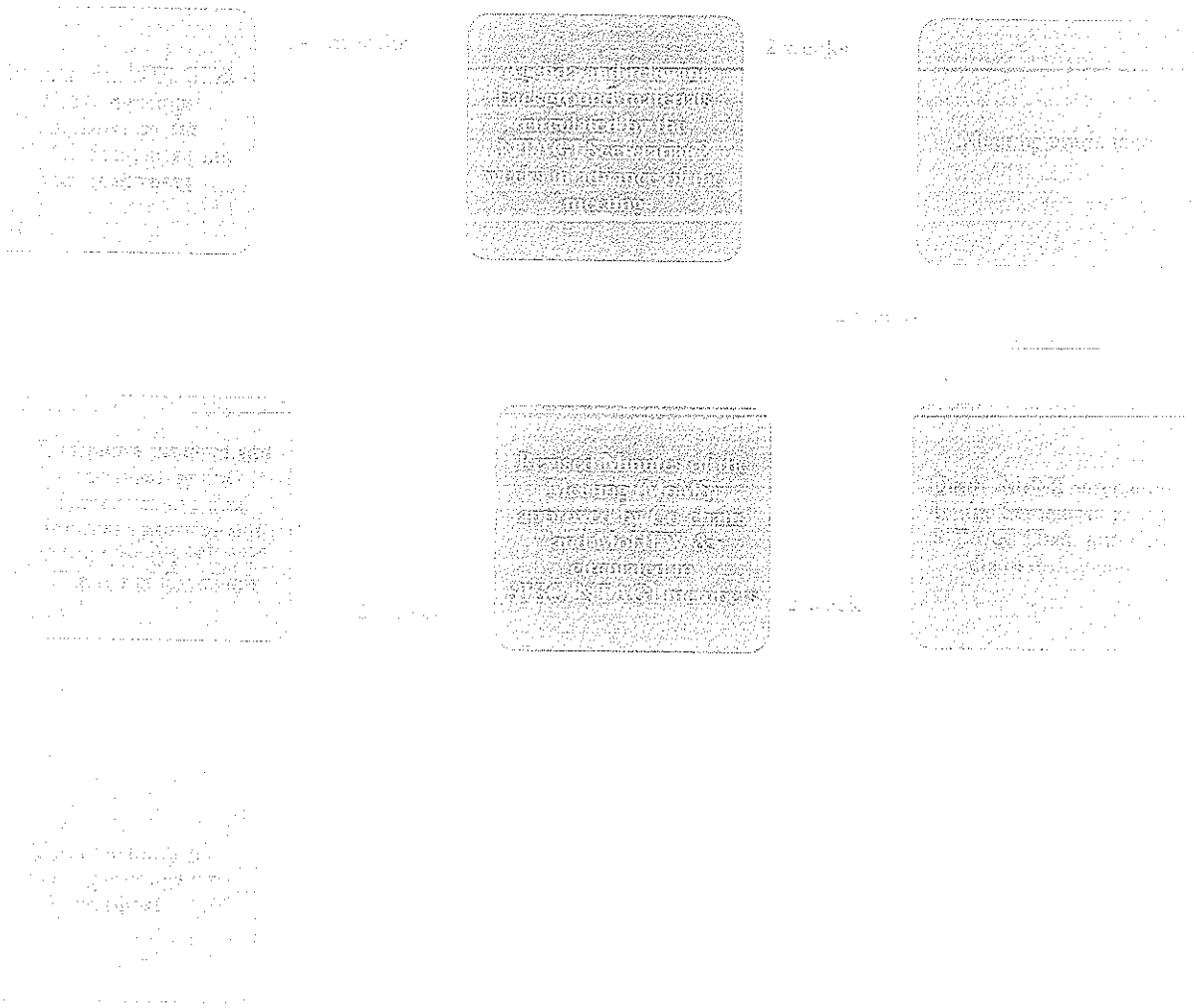
49. The agenda will usually include at least one standing agenda item, review of evidence on topics set by the NTAGI in advance, response to topical issues that arise following the previous meeting and horizon scanning of items for future discussion based on public health needs of the country.

50. The Secretariat is responsible for the timely recording and dissemination of meeting minutes and recommendation. The ratification of the minutes of the meeting will be done through circulation of minutes amongst the members. A schematic for preparation, recording and dissemination of meeting materials is described below in Box 1 under the standard operating procedures for the meeting.

51. NTAGI minutes should be circulated within two weeks after the meeting for comment by the members and simultaneously by the co-Chairs and MoHFW. The minutes and comments will be reviewed and finalized within a further two weeks by the co-Chairs and MoHFW and published under the NTAGI link at the websites of the following departments:

    - Ministry of Health & Family Welfare website
    - Indian Council of Medical Research
    - Department of Biotechnology

52. STSC minutes must be circulated to the NTAGI to allow for free and open debate on issues discussed. Once the NTAGI minutes are made public, the relevant STSC minutes should also be made public.



Box 1: Schematic for standard operating procedures for meetings

Participation in the meetings

53. All meetings are considered closed-door, with the exception of special invitees. These non-members will be vetted by the Chair and Co-chairs and the MoHFW before they attend a meeting. Special invitees will be allowed to participate in technical capacities and discussions, but

must exit before decision-making or voting occurs. Manufacturers may occasionally be invited to contribute to the discussion and inform the NTAGI or STSC about the products but will not be allowed in the closed-door sessions when recommendations are being formulated. If and when manufacturers are invited to observe meetings, the setting and handling must prevent undue influence by these manufacturers, while maintaining proprietary data confidentiality.

54. Crafting and adoption of recommendations will always be strictly closed-door. This allows members to have free and open debate before coming to any conclusions, which will be fully and clearly explained in minutes or statements.

55. The NTAGI Secretariat support staff attend meetings in order to facilitate and to record minutes. These staff remain throughout the discussion and approval of recommendations, but do not participate in the discussion, recommendations, or voting.

56. When a member does not attend a meeting or attends a portion of a meeting, the member is provided background material on the issues discussed, and is expected to be prepared to participate in the next meeting.

Responsibilities of NTAGI Chair, Co-chairs and Core Independent Members

Responsibilities of Chair and Co-chairs

57. The Chair should provide effective leadership, in particular:

A) Ensuring that the NTAGI and the STSC carries out its function effectively and does not exceed its powers or functions.

B) Ensuring that the minutes of the meetings and any reports accurately record the views of the NTAGI or STSC.

C) Ensuring that views of the NTAGI are accurately represented when providing information to the general public and press.

D) Providing performance management of the NTAGI members.

E) Ensuring that the NTAGI manages any conflicts of interest appropriately.

F) Ensuring availability for guidance to the Secretariat in case of urgent request for advice on technical matters related to immunization services.

Responsibilities of NTAGI and STSC members

All members of the NTAGI and its Sub-committee must demonstrate a high standard of conduct in exercising their duties.

Attendance at meetings

58. Except in the event of an emergency, meeting dates for NTAGI and STSC are published a year in advance. It is the responsibility of the Committee members to attend all meetings. At the discretion of the NTAGI Chair and Co-chairs, a member may be linked to a meeting by telephone or videoconference, in which case their presence shall count towards the quorum.

59. Failure by a member to attend three meetings in a row without prior notice or subsequent explanations to the NTAGI Chair and Co-chairs may constitute grounds for termination of appointment of the member, to be decided at the discretion of the NTAGI Chair and Co-chairs. Members may also resign from the NTAGI and its STSC if they wish.

Declaration of interests

60. The purpose of the declaration of interest form is to protect the NTAGI and its constituents from possible conflicts of interest ensuring that, in principle, decisions made by the NTAGI are free from any external influences, either personal or fiduciary, whilst recognizing that it is precisely their position and expertise external to the NTAGI that enables certain individuals to make valuable contributions to its work. All members of the NTAGI,the STSC and the NTAGI Secretariat, as well as special invitees that attend the meeting, must follow the rules set out in this document regarding the declaration of interest [Annexure 2].

61. A member must abide by the following rules when deciding whether to declare an interest:

A) **Personal pecuniary interests:** If a member has in the last four years received or plans to receive a financial payment or other benefit from a business or a representative body relating to vaccines or any other product of service that is specific to an agenda item under consideration by the NTAGI or its STSC, the member may be allowed to participate in the discussion, but not in any subsequent vote or decision making process. If the interest is not specific to an agenda item (i.e. payment relates wholly to other products), the member will be able to participate in both, the discussion and the vote. The main examples for personal pecuniary interests are explained below:

   i) Consultancies - any consultancy, directorship, position in or work for the industry, which attracts regular or occasional payments in cash or kind.

ii) Fee-paid work -any work commissioned by the industry for which the member is paid in cash or kind.

iii) Shareholdings - any shareholding in or other beneficial interest in shares of the industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management.

B) Personal family interest: If a family member of a current NTAGI or STSC member, has in the last four years received or plans to receive a financial payment or other benefit from a business or a representative body relating to vaccines or any other product of service that is specific to an agenda item under consideration by the NTAGI or its STSC, the member may be allowed to participate in the discussion, but not in any subsequent vote or decision making process. If the interest is not specific to an agenda item (i.e. payment relates wholly to other products), the member will be able to participate in both, the discussion and the vote.

C) Non-Personal pecuniary interests: A non-personal interest involves payment, which benefits a department for which a member is responsible, but is not received by the member personally. If the interest is specific to an agenda item, a member may be allowed to participate in the discussion and subsequent vote, at the discretion of the NTAGI Chair and Co-chairs. If the interest is not specific to an agenda item, and instead related wholly to other products, the member may be allowed to participate in the discussion and subsequent vote. However, members are under no obligation to seek out knowledge of work done for or on behalf of the industry within departments for which they are responsible if they would not normally expect to be informed. Main examples are:

i) Fellowships - the holding of a fellowship endowed by the industry.

ii) Support by the industry - any payment, other support or sponsorship by the industry which does not convey any pecuniary or material benefit to the member personally but which does benefit their position or department; for example:

- A grant from a company for the running of a unit or department for which the member is responsible
- A grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which the member is responsible. This does not include financial assistance for students;
- The commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsible.

62. Members must declare all their interests at the time of their appointment and must promptly notify the NTAGI Chair, Co-chairs and the Secretariat of any changes. Before or at the start of every meeting, members will be asked to declare any changes to their interests and the minutes of each meeting will include interests that are declared and how they have been handled. In addition, it is the responsibility of each member to indicate if they have an interest in any item of business on the agenda of a meeting of NTAGI or its STSC at the appropriate time. Where this happens, in accordance with the provisions below, the Chair will determine whether a member should take part in any discussion or decision on an issue.

63. Members are not under an obligation to search out links between one company and another, for example where a company with which a member is connected has an interest in another company of which the member is not aware and could not reasonably be expected to be aware of.

64. Where members are uncertain as to whether an interest should be declared, they should seek guidance from the NTAGI Chair and Co-chairs and the Secretariat. If members have interests

not specified in these notes but which they believe could be regarded as influencing their advice they should declare them. Interests are considered relevant if they occurred within the last four years. The Secretariat is responsible for maintaining and updating records of member's relevant interests.

Confidentiality agreement

65. The NTAGI and STSC deal with confidential information and meetings are not open to public, as noted above. To maintain due process of decision making, members must abide by the confidentiality undertaking [Annexure 3] detailed below:

A) Commercial, academic and other research institutions and individual scientists may submit or present for discussion to the NTAGI STSC members, on research, products and processes (hereafter referred to as "Information") which the institutions and individuals consider proprietary. To help ensure the appropriate use of such information by STSC members whilst protecting the institutions' or individual's proprietary rights, the Secretariat will undertake to release such Information only to persons who have signed this agreement.

B) Information submitted by such institutions or individuals through NTAGI Secretariat to committees to inform their discussions shall be regarded by the Undersigned as confidential, unless clearly stated otherwise, by the institution, individual concerned and/or the NTAGI Secretariat.

C) The Undersigned undertakes to treat such confidential Information as proprietary information and agrees not to make copies of it, nor to disclose or use the same in whole or in part.

D) If requested to do so, the Undersigned agrees to return to the NTAGI Secretariat any and all Information identified as confidential.

E) The Undersigned shall not be bound by confidentiality if he/she is able to demonstrate that

the Information:

a. Was known to him/her prior to any disclosure to him/her by the NTAGI Chair, Co-chair or Secretariat;

b. Was in the public domain at the time of disclosure by the NTAGI and its Secretariat;

c. Becomes part of the public domain through no fault of the Undersigned;

d. Becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality.

F) Proceedings of the NTAGI Committee meetings shall be confidential and no member who is not authorized by the NTAGI Chair or Co-chairs via the Secretariat is to speak on its behalf shall communicate externally about the discussion, decision and opinions expressed by the Committee or STSC, or by individual members during the course of this meeting, on a public or private forum. In signing below the undersigned undertakes to hold confidential what is shared and discussed within the NTAGI meeting.

G) The minutes of the meeting will be released by the NTAGI Secretariat in the public domain within six weeks of each meeting, but will not contain any confidential information as defined by the clauses previously stated.

H) This Confidentiality Undertaking is valid during the entire time the Undersigned participates in the work of the NTAGI, in whatever capacity, and for a period of five (5) years thereafter.

Communications with media

66. Members of NTAGI or STSC should not speak to the media as representatives of the NTAGI or STSC, unless the NTAGI Chair and Co-chairs designate a member to speak for the Committee. Members should inform the NTAGI Chair, Co-chair and the NTAGI Secretariat of all relevant contacts with the media. An NTAGI member may discuss with the media an issue

that has also been discussed at NTAGI, but should take care to explain that he/she is discussing it in an individual professional capacity and not as a member of NTAGI or on behalf of NTAGI or its STSC. No member should reply to official correspondence on behalf of the NTAGI without consulting the Secretariat. The only exception to this rule is that all members are free to respond to questions about established points of fact (e.g., meeting dates, citations for NTAGI recommendations, etc.)

67. NTAGI and STSC members may be solicited to participate in consultations or surveys on vaccine issues that are addressed by the NTAGI. Members can respond in their individual capacities on their areas of expertise, but should refer any questions related to specific topics discussed by NTAGI to the co-Chairs. For research studies, members should not exercise undue influence to elicit participation in national/regional/global studies on account of their NTAGI membership.

68. Members are prohibited from making any speech or producing a publication in which the purpose is to report on the member's work on the NTAGI, without the written permission of the co-Chairs. Voting members should be concerned with and report to the Secretariat, and solicitation of information about the NTAGI or STSC's activities by persons not officially affiliated with the NTAGI or STSC.

Accountability

69. Members are free to maintain associations with trade unions, co-operative societies, trade associations etc. to the extent that such associations do not conflict directly with the interest of the NATGI or STSC. If members have any doubt about any of these matters, advice should be sought from the Chair/Co-chair/Secretariat.

70. Any legal proceedings initiated by a third party are likely to be brought against the NTAGI as a whole, although in exceptional cases proceedings (civil or, in certain cases, criminal) may be brought against the Chair or individual members.

71. If a member is at any time unclear whether or not an action in contemplation would be classified as duties as members of NTAGI or its STSC he or she should clarify this with the Secretariat or co-Chairs.

72. NTAGI advice may be used by Government health departments or public health bodies in India. Any legal challenge to any action taken on the advice or recommendations of the Committee will be the responsibility of that department and not the NTAGI.

Process for evidence review and developing recommendations

73. The NTAGI will deal with evaluation of issues relevant to a new immunisation programme or major changes to, or discontinuation of, an existing immunisation programme

74. The evaluation of potential changes to the immunisation programme will usually proceed through the following steps:

    A) Defining the policy question

    B) Evidence gathering by the Secretariat and working group

    C) Working group consultation with experts and review and synthesis of evidence

    D) Evidence review by the STSC

    E) Recommendations of the STSC presented to the NTAGI

    F) NTAGI review and final recommendations

These steps are described in detail below:

A) First, the Secretariat in consultation with the Chairs and co-chairs, MoHFW and STSC working group members (where relevant) will frame the policy question(s). The issue(s) may

be based on a request for advice made by the MoHFW or identified by horizon scanning. If no working group exists, the co-Chairs, in consultation with the MoHFW will constitute an ad-hoc working group and present them with their charge.

B) Second, the ad-hoc working group for the issue and the Secretariat identify and collate relevant evidence. Evidence gathering may proceed in a number of ways, including by a systematic literature review which involves searching a wide range of medical and scientific databases, a call for evidence from stakeholders, and/or a commission issued for an impact and cost effectiveness study. This body of information will often include submissions on the safety and effectiveness of, and other information on, specific vaccines from vaccine manufacturers that may be commercially confidential. The working group may consult with independent subject matter experts, key immunization partners and research institutes as well as private vaccine manufacturers to generate a comprehensive body of evidence that will allow the relevant question to be answered, highlight any important gaps in the evidence, and identify and evaluate alternative policies (including the no-action or no-change options).

C) Third, the STSC will meet to analyse the evidence that is synthesized and presented by the working group and any external subject matter experts whose contribution the working group considers essential. The STSC members will review the evidence, discuss the recommendations of the working group, and agree upon a report/recommendation to be given to the NTAGI.

D) Fourth and finally, the NTAGI may review and approve the STSC recommendations. In making such recommendations, the NTAGI will take into account all available information about a vaccine, as well as the larger context of the health care delivery systems in India, the current epidemiology of the disease, implementation issues, ethical and legal constraints, and other factors.

75. A robust, systematic framework based on internationally agreed protocols will be used for evidence review and developing recommendations. Regular review of available methodology will fall under the purview of the standing working group on research and capacity building of the NTAGI.

76. Advice or recommendations will normally be formulated during the course of the meetings usually by consensus. If consensus is not reached and at the discretion of the Chair and Co-chairs, voting may occur. A majority is needed for approval of any recommendation and dissents will be noted in the meeting minutes. At least half of the voting members must be present for quorum and for voting to occur, although the Co-chairs may allow for exceptions in emergency circumstances.

77. At the discretion of the Chair and Co-chairs, a member may be linked to a STSC or NTAGI meeting by telephone or videoconference, in which case their presence shall count toward the quorum.

Reporting, recording and dissemination of recommendations

78. The NTAGI and its STSC are committed to making as much of its work open to public scrutiny as possible. However, there is a generic understanding that scientific advisory committees will treat unpublished research in confidence until it has been peer-reviewed and published in the scientific or medical literature, unless the investigators give specific permission for pre-publication release, as explained in the confidentiality section para 61 of this document. This helps ensure that the Committee has access to as much of the relevant, but unpublished, data as possible.

79. NTAGI and STSC advice and recommendations are published in the minutes of meetings. Where advice or recommendations relate to a new vaccination programme, or revisions to an existing vaccination programme, these are also published in an official statement on the NTAGI

web-links, crafted by the Secretariat in consultation with the NTAGI Chair and Co-chairs and the relevant working group.

80. In addition to meeting minutes and recommendations, the NTAGI aims to publish the following documents: Code of Practice, Frameworks for evidence review and systematic development of recommendations, meeting calendar and agenda, statements, annually updated recommended schedule for vaccines included in the UIP and register of members' interests. The NTAGI will publish a position paper for each vaccine included in the UIP as soon as feasible, but preferably within one year of the recommendation for inclusion being made.

ANNEXURES: CODE OF PRACTICE

The annexures below comprise forms for use for all members of the National Technical Advisory Group on Immunization and the Standing Technical Sub-committee as well as special invitees attending NTAGI and STSC meetings.

Annexure 1: Declaration of agreement to Code of Practice, including Confidentiality agreement

DECLARATION

I have read and understood the NTAGI Code of Practice. I agree that I will abide by the NTAGI code of practice for:

a) The period of time I am a NTAGI member/ a NTAGI Sub-committee member/ an invited observer.

b) In respect of confidentiality, thereafter for such periods of time as information communicated in confidence is not disclosed by authority.

SIGNED

SURNAME (BLOCK LETTERS)

FORENAME (BLOCK LETTERS)

DATE

Annexure 2: Declaration of Interests

As a new member of the NTAGI/STSC, please ensure you have read and understood the Code of Practice. We would appreciate your answers to the following questions:

1. Who is your primary employer? _____

2. Do you have any grants that are funded by vaccine manufacturers? Yes/No. If yes, what is the nature of the grant (e.g., research, education) and what is your role (e.g., PI, supervisor)?

_____

3. Do you, your spouse or dependent children own stock in any vaccine manufacturer or parent company of a manufacturer? If yes, what manufacturer(s)/company (ies)?

_____

4. Do you have a patent on any vaccine or candidate vaccine? Yes/No. If you are not the patent holder, are you otherwise entitled to royalties or other compensation from such a patent?

_____

5. Do you serve in any advisory role with a vaccine manufacturer (e.g., serving as a member of or consultant to a manufacturer's advisory committee)? Yes/No. If yes, what is the nature of this role?

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6. During the past year, have you received any honoraria or travel funds from vaccine manufacturers (or from educational grants from vaccine manufacturers) for presentations at scientific meetings? If yes, what was the nature of the meeting (e.g., professional society meeting, manufacturer forum)?

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7. Do you serve in any fund-raising role with any organization that could involve solicitation of funds from vaccine manufacturers? If yes, please describe your role.

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8. Have you done any consultation with law firms for vaccine-related litigation? Yes/No

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9. Have you any interests, as detailed in paragraphs 56-60 of the NTAGI Code of Practice document which may be considered as constituting a real, potential or apparent conflict of interest?

Yes: **No:** **If yes, please give details in the box below.**

Type of interest (refer para 54 of Code of Practice for details)	Name of commercial entity	Belongs to you, partner or unit?	Current interest? (or year ceased)

10. Is there anything else that could affect your objectivity or independence in the meeting or work, or the perception by others of your objectivity and independence?

_____

_____

I hereby declare that the disclosed information is correct and that no other situation of real, potential or apparent conflict of interest is known to me. I undertake to inform you of any change in these circumstances, including if an issue arises during the course of my engagement with the NTAGI or its STSC.

_____ _____

Signature Date

_____ _____

Name Institution

Annexure 3: Confidentiality Agreement

1. Commercial, academic and other research institutions and individual scientists may submit or present for discussion to the NTAGI Standing Technical Sub-committee (STSC) members, on research, products and processes (hereafter referred to as "Information") which the institutions and individuals consider proprietary. To help ensure the appropriate use by STSC members of such Information whilst protecting the institutions' or individual's proprietary rights, NTAGI Secretariat will undertake to release such Information only to persons who have signed this agreement.
2. Information submitted by such institutions or individuals through NTAGI Secretariat to committees to inform their discussions shall be regarded by the Undersigned as confidential, unless clearly stated otherwise, by the institution, individual concerned and/or the NTAGI Secretariat.
3. The Undersigned undertakes to treat such confidential Information as proprietary information

and agrees not to make copies of it, nor to disclose or use the same in whole or in part.

4. If requested to do so, the Undersigned agrees to return to the NTAGI Secretariat any and all Information identified as confidential.

5. The Undersigned shall not be bound by confidentiality if he/she is able to demonstrate that the Information:

   a) Was known to him/her prior to any disclosure to him/her by the NTAGI Secretariat;

   b) Was in the public domain at the time of disclosure by the NTAGI Secretariat;

   c) Becomes part of the public domain through no fault of the Undersigned;

   d) Becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality.

6. Proceedings of the NTAGI and its STC meetings shall be confidential and no member who is not authorized by the NTAGI Secretariat to speak on its behalf shall communicate externally about the discussion, decision and opinions expressed by the Committee or STSC, or by individual members during the course of this meeting, on a public or private forum. In signing below the undersigned undertakes to hold confidential what is shared and discussed within the NTAGI meeting.

7. The minutes of the meeting will be released by the NTAGI Secretariat in the public domain within six weeks of each meeting, but will not contain any confidential information as defined by the clauses previously stated.

8. This Confidentiality Undertaking is valid during the entire time the Undersigned participates in the work of the NTAGI, in whatever capacity, and for a period of five (5) years thereafter.

Signature..... Name.....

REFERENCES

1. Advisory Committee on Immunization Practices. 2002. *ACIP Policies & Procedures.* Georgia, Atlanta, USA

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3. John, T. Jacob. 2010. «India's National Technical Advisory Group on Immuniztion.» *Vaccine.* doi:10.1016/j.vaccine.2010.02.041.

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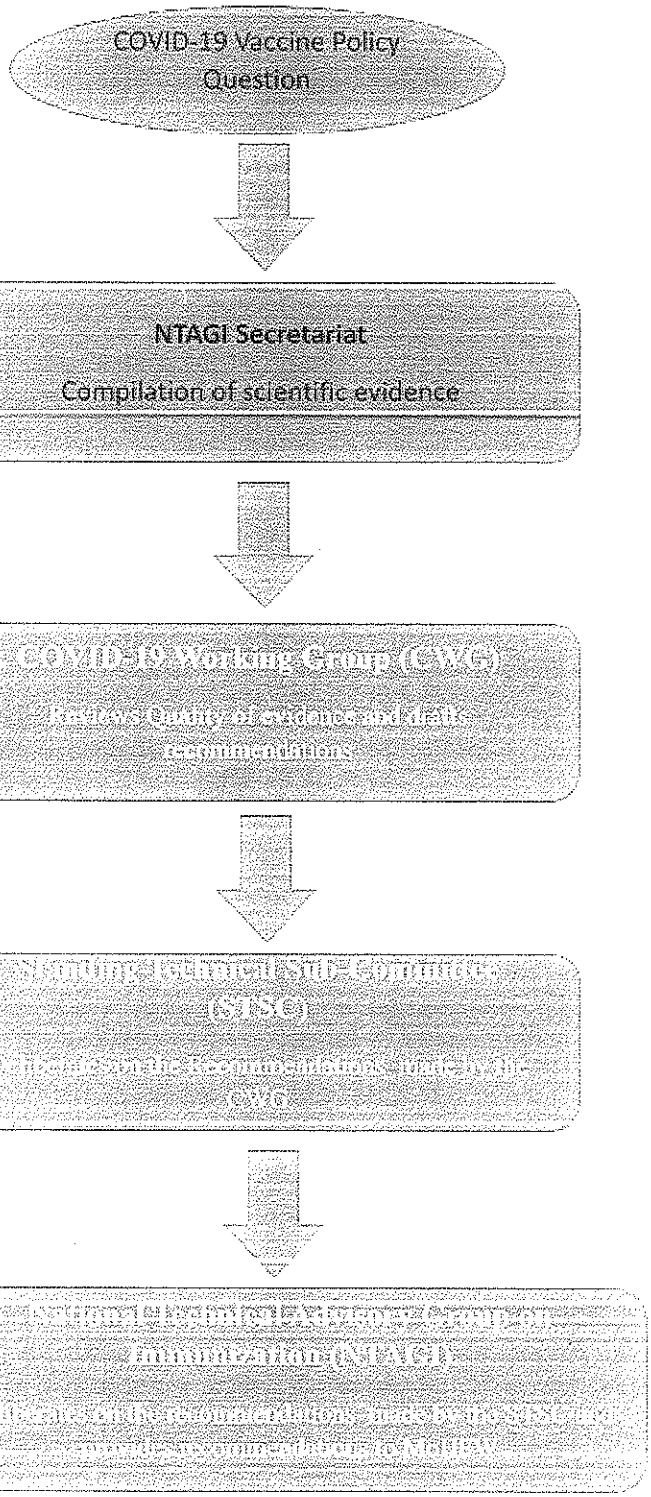
Annexure – A8

Work Flow of the NTAGI on COVID-19 Vaccines



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Annexure-A9

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.

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215 Annexure – A10

Flow chart for reporting of AEFI-COVID

Reporting of AEFI in CoWIN by designated person

Vaccinator*

District Immunization Officer (DIO)

MOs, private practitioners, other health staff

Case is reported in CoWIN using basic information of the event

*Note- Vaccinated beneficiary are observed for 30 min post vaccination at the session site to oversee if any allergic adverse event that may occur following vaccine.

Moreover, any vaccinated beneficiary can report a suspected adverse event irrespective of the time duration post vaccination

Once reported the case is verified by the DIO as Minor, Severe and Serious

For all the severe and serious AEFI cases, CRF (Case Reporting Form) and CIF (Case Investigation Form) form is filled and uploaded on COWIN along with relevant clinical records (hospital records or post mortem report/verbal autopsy form)

Causality assessment of serious/severe AEFI cases is done by the trained medical experts of the state / national level

Causality results discussed and approved by the national AEFI committee is put up on MoHFW website in public domain

Convergence with stakeholders- There is a strong convergence with the Pharmacovigilance Programme of India (PvPI) under Indian Pharmacopoeia Commission (IPC) for exchange of information regarding reported cases from the 250 Adverse Drug Reaction Monitoring Centres in Medical Colleges and large hospitals. Information from PvPI and CDSCO are collated and studied in case of any new, previously unknown events identified through AEFI surveillance.

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216 Annexure-A11

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.

(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

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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.
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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.

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Annexure-A12

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.

Yours sincerely

(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

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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				

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Annexure-A13

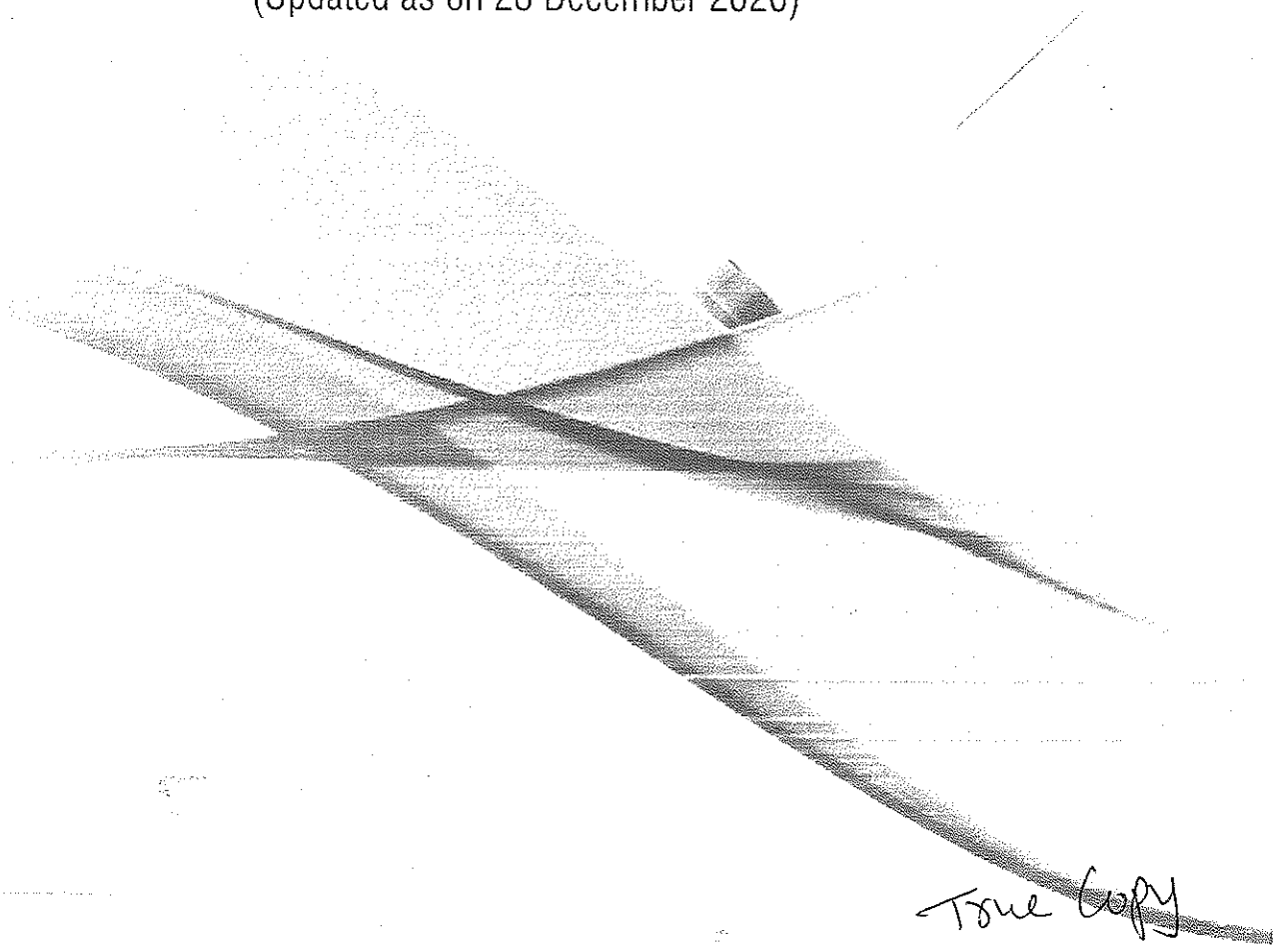
सत्यमेव जयते

Ministry of Health & Family Welfare
Government of India

COVID-19 VACCINES

TRAINING GUIDELINES

(Updated as on 28 December 2020)



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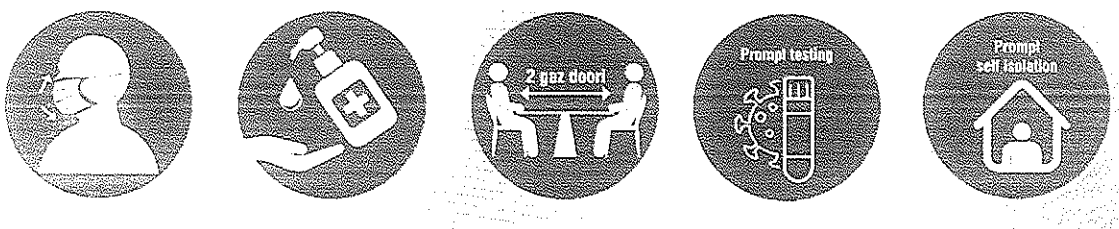


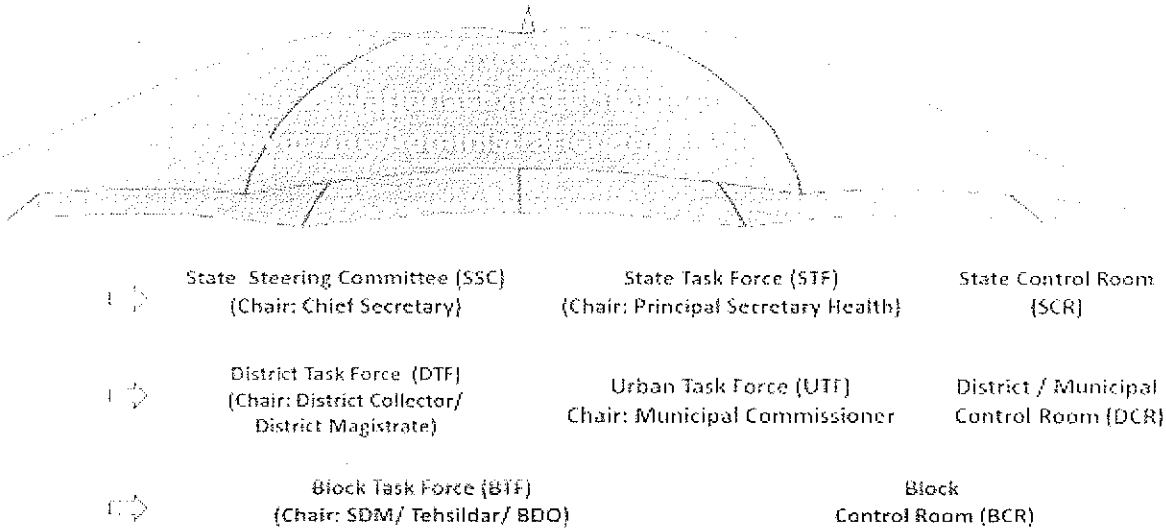
24x7 helpline no. 1075 (Tollfree)
www.mohfw.gov.in | www.cowin.gov.in

1. EXECUTIVE SUMMARY

Coronavirus disease (COVID-19), is an infectious disease caused by a newly discovered coronavirus (SARS-CoV-2), which has spread rapidly throughout the world. In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. The pandemic has severely ravaged health systems, and economic and social progress globally.

In India, 96,06,810 confirmed COVID-19 cases and over 1,39,700 deaths have been reported as of 4 December 2020.[1] COVID-19 most commonly manifests as fever, dry cough, shortness of breath and tiredness. Most people (~80%) experience mild disease and recover without hospitalization, while around 20% may become more seriously ill.

While countries, including India, have taken strong measures to contain the spread of COVID-19 through better diagnostics and treatment, vaccines will provide a lasting solution by enhancing immunity and containing the disease spread. In response to the pandemic, the vaccine development process has been fast-tracked. Globally, over 274 candidate vaccines are in different stages of development as of 4 December 2020.[2] The majority of vaccines in clinical evaluation as of 4 December 2020 will require a two-dose schedule to be administered two, three or four weeks apart, and is need to be administered through the intramuscular route.[3]



Anticipating that the COVID-19 vaccine may soon be available, the Government of India (GoI) is preparing for its it to be introduced in the country so that it can be expeditiously rolled out when available.

One of the milestones in this direction has been the constitution of a National Expert Group on Vaccine Administration for COVID-19 (NEGVAC). The NEGVAC will guide all aspects of the COVID-19 vaccine introduction in India.

1 https://www.mohfw.gov.in/ accessed 4 December 2020

2 https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/ accessed on 4 December 2020

3 https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines, accessed 4 December 2020

High-level coordination at the national, state and district levels must be established for effective cooperation and collaboration among the key departments. 19 ministries at national level, 23 departments at state/ district and numerous developmental partners are involved in planning the COVID-19 vaccine introduction; their roles have been described in these operational guidelines.

The Successful introduction of the COVID-19 vaccine will largely depend upon the quality of training conducted for enumerators for beneficiary listing, health functionaries for vaccination activities, social mobilizers for all mobilization activities and communication training for all workers involved in the process of vaccination. As demonstrated during recent experiences with pneumococcal conjugate vaccine (PCV) introduction and polio supplementary immunization activities (SIAs) conducted during the COVID-19 pandemic, national and state training of trainers (ToT) may be successfully conducted on virtual platforms and cascaded to district and sub-district levels using a mix of virtual and face-to-face training. The COVID-19 vaccine will be introduced once all training is completed in the district/block/planning unit.

COVID-19 vaccine will be offered first to healthcare workers, frontline workers and population above 50 years of age, followed by population below 50 years of age with associated comorbidities based on the evolving pandemic situation, and finally to the remaining population based on the disease epidemiology and vaccine availability. The priority group of above 50 years may be further subdivided into those above 60 years of age and those between 50 to 60 years of age for the phasing of roll out based on pandemic situation and vaccine availability. The latest electoral roll for the Lok Sabha and Legislative Assembly election will be used to identify the population aged 50 years or more.

The COVID-19 Vaccine Intelligence Network (Co-WIN) system, a digital platform will be used to track the enlisted beneficiaries for vaccination and COVID-19 vaccines on a real-time basis. At the vaccination site, only pre-registered beneficiaries will be vaccinated per the prioritization, and there will be no provision for on-the-spot registrations.

Based on the numbers of registered beneficiaries and the priority accorded, vaccination sessions will be planned with the following considerations:

- One session for 100 beneficiaries;
- While most of the healthcare and frontline workers would be vaccinated at fixed session sites that may be government health facilities above PHCs or private health facilities identified by district administration, vaccination of other high-risk populations may require outreach session sites, and mobile sites/teams; and
- State/UT can identify specific days for vaccination;
- The entire vaccination process will be broadly similar to the election process.
- The vaccination team will consist of five members as follows:
  - **Vaccinator Officer**–Doctors (MBBS/BDS), staff nurse, pharmacist, auxiliary nurse midwife (ANM), lady health visitor (LHV); anyone authorized to administer an injection may be considered as a potential vaccinator;
  - **Vaccination Officer 1:** At least one person (Police, home guard, civil defense, national cadet corps (NCC), national service scheme (NSS), endr yuva kendra sangathan (NYKS) who will check the registration status of a beneficiary at the entry point and ensure the regulated entry to the vaccination session;
  - **Vaccination Officer 2:** Is the verifier who will authenticate/verify the identification documents; and
  - **Vaccination Officer 3 & 4** are the two-support staff who will be responsible for crowd management and ensure 30 minutes of waiting time by beneficiary post-vaccination. Support staff will provide information, education and communication (IEC) messages and support to vaccinator as well as the vaccination team.

Essential health services including existing routine immunization sessions should not be impacted or interrupted.

Vaccine safety need to be ensured during storage, transportation and delivery of vaccine with sufficient police arrangements so that there are no leakages in the delivery system.

Safety precautions, including infection prevention and control practices, safe injection practices and waste disposal, will be followed during vaccination sessions. As large population groups will be vaccinated over a short period with a new vaccine, monitoring the safety of these vaccines will be critical. The existing adverse events following immunization (AEFI) surveillance system will be utilized to monitor adverse events and understand the safety profile of the vaccines. To ensure confidence in the vaccine and the immunization programme during COVID-19 vaccine introduction, states/UTs must rapidly detect and promptly respond to all AEFIs. The reporting of AEFI through surveillance and action for events following vaccination (SAFEVAC) has been integrated with Co-WIN software and every AEFI to be reported at the district level and facilitate the referral mechanisms in case any AEFI needs to be put in place.

Requirements for **management of the cold chain** for COVID-19 vaccination will vary depending on the type of COVID-19 vaccine, as different vaccines have different storage temperature ranges. Cold chain assessments and gap analysis have been completed, and there are plans in place for supplying additional cold chain equipment where required. States/UTs must ensure adequate cold chain storage capacity for the COVID-19 vaccine campaign. Cold chain handlers, and vaccinators at all levels will be trained on procedures for vaccine and logistics management as well as infection prevention and control precautions.

Every effort is being made to ensure that everyone in the country has access to timely, accurate and transparent information about the COVID-19 vaccine(s). This requires a meticulous, structured, informative and clear communication strategy to create adequate awareness, ensure accurate knowledge, generate and manage adequate demand, facilitate eagerness and address vaccine hesitancy and confidence, and mitigate for unintended situations (e.g. AEFI clusters, delay in vaccine roll-out for certain population categories) to ensure the smooth introduction and roll-out of COVID-19 vaccine(s). Key communication and demand generation strategies include advocacy at national, state, district and sub-district levels; capacity building, media engagement, social mobilization and partnership, community engagement and empowerment is included at family and community levels. Key areas to be addressed in the communication plan includes information on COVID-19 vaccine, vaccine eagerness, vaccine hesitancy and COVID-19 appropriate behavior.

A vaccination programme of this scale will require close monitoring and supportive supervision at all levels to identify bottlenecks and challenges faced at the ground level. Each step-in the vaccine introduction will be monitored. This includes:

- **Tracking the progress of introduction activities** – beneficiary registration training, vaccine logistics availability, and task forces. This will be supported by partners through tracking mechanisms;
- **Readiness assessment before vaccine introduction** – field visits and desk review of data at national and state levels;
- **Concurrent monitoring of vaccination activities** – daily evening meetings, standardized monitoring tools, mobile-based apps, real-time data from the planning unit to the national level; and
- **Knowledge management** – the best practices and innovations at all levels would be shared to improve the implementation in the next phase of scale-up.

10. ADVERSE EVENTS FOLLOWING IMMUNIZATION

COVID-19 vaccines have limited safety data. Therefore, it is important to monitor the safety of these vaccines when administered to a large population. A robust AEFI surveillance system would enable us to monitor adverse events and better understand the safety profile of the vaccines. During COVID-19 vaccinations, AEFIs must be rapidly detected and promptly responded to or else it can undermine confidence in the vaccine and immunization programme. All AEFIs should be reported as per the National AEFI Guidelines.

Programme managers should be aware of the following:

- COVID-19 vaccination will involve vaccination of large population over a short period of time. This may lead to increased reporting of AEFIs;
- During mass campaigns, there can be chances of anxiety reactions and occurrence of programme errors, especially if it involves reconstitution of vaccines using diluents; and
- Immunization errors which might lead to AEFI must be prevented at all costs through proper training, regular and intensive monitoring and supervision, and strict adherence to proper vaccine / diluent handling procedures and injection practices.

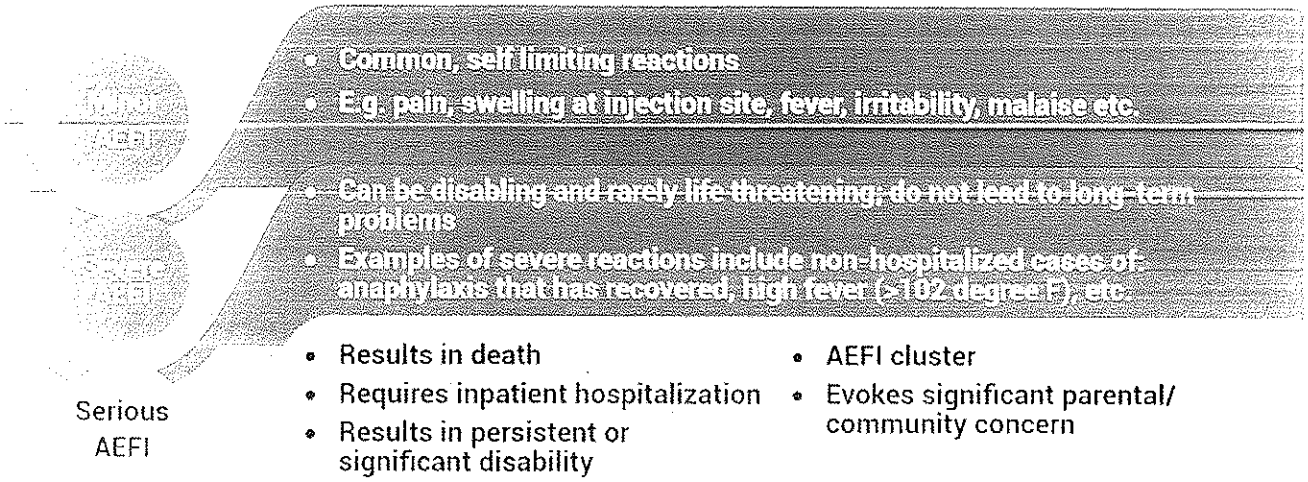
COVID 19 vaccines may be administered to persons belonging to high risk groups such as health care workers, other front line workers such as those in the police, municipal workers, etc. who are more at risk of contracting the disease and the elderly and persons with co-morbidities as they are more likely to have higher mortality and morbidity rates as compared to healthy individuals. Many of the deaths, and hospitalizations following COVID19 vaccinations in these high-risk groups may be coincidental. However, it is important that all deaths, hospitalizations, any event occurring in clusters following COVID19 vaccination, or any event felt by health workers and medical staff to be due to COVID 19 vaccines or vaccinations should be reported and investigated immediately.

The overall goal of AEFI surveillance is to ensure that vaccines are administered safely to the recipients and the trust in vaccines is sustained. The specific objectives of AEFI surveillance are to:

- Promptly detect, report and respond to AEFIs;
- Promptly identify programmatic errors and implement corrective measures;
- Document the rates of AEFI for a specific vaccine lot / brand in a specific region/population;
- Estimate serious AEFI rates in the population and compare these with local and global data;
- Identify signals of unexpected adverse events that would need further confirmation and planned studies; and
- Sustain confidence of the public, health functionaries and professionals on the vaccines and immunization program.

An adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended disease, symptom, sign or abnormal laboratory finding. Reported adverse events can either be true adverse events, i.e. really a result of the vaccine or immunization process, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization.

For purposes of reporting, AEFIs can be classified as minor, severe and serious



PREVENTION OF AEFIs

Injectable COVID-19 vaccines are expected to be given in a campaign mode and these vaccines may have different modalities of administration. Appropriate measures need to be taken to avoid possibilities of anxiety reactions in individuals and clusters. Programme managers and implementers must plan to prevent and minimize chances of occurrence of preventable AEFIs. Beneficiaries should be observed at the session site for at least 30 minutes post-vaccination to detect, manage and treat immediate adverse reactions.

PREVENTING ANXIETY REACTIONS

Session sites should be planned in such a way that there is a separate area for those waiting for vaccination, site of actual vaccination and post-vaccination observation area.

- Ensure vaccinations occur in comfortable, well-ventilated and airy settings. Beneficiaries who seem anxious or nervous should be identified and made to calm down or their attention diverted from the process and the pain. After vaccination, they should be asked to remain seated for some time and observed. If they feel light-headed or giddy, they should be asked to lie down for some time.

PREVENTING PROGRAMME ERRORS

Ensure guidelines for safe injection practises are followed at the session site. Special attention should be on the following:

- Ensure nothing other than vaccines / diluents are stored in ILRs;
- If reconstitution is required, separate reconstitution syringes should be used for each vial and diluent;

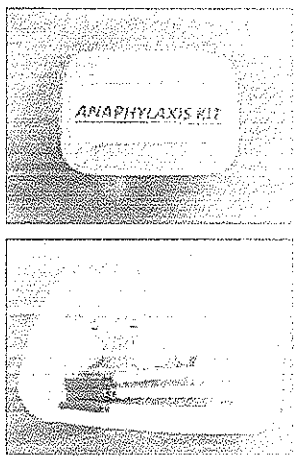
- Proper cold chain management of the vaccines at the session site;
- Screening for contraindications of the vaccine; and
- Other specific precautions as per guidelines issued or as mentioned in the vaccine product insert.

Vaccinators and supervisors at the vaccination site will provide primary treatment of all AEFIs. If needed, cases should be immediately referred to the nearest AEFI management centre/ health facility and reported to the appropriate authority.

COVID 19 vaccination sessions may be at fixed sites such as at government health facilities such as PHCs, urban PHCs, CHC, Sub divisional hospitals, district hospitals, medical college hospitals and identified private hospitals and nursing homes, etc. or in outreach.

- All beneficiaries must be counselled about adverse events which may occur after COVID-19 vaccine. These are expected to be minor events such as local pain and swelling and mild to moderate fever, etc. However, the list of expected events could be different based on the safety profile of the COVID19 vaccine(s) which finally gets approved for use.
- In case of any type of discomfort or illness following COVID vaccination, the vaccine recipient should visit the nearest health care facility for treatment.
- At fixed session sites, an AEFI management kit or an emergency tray should be available for use. The contents of the AEFI kit are: Inj. Adrenaline (1:1000) (3), Inj. Hydrocortisone (3), Ringer lactate/Normal saline (2), 5% dextrose (2), IV drip set (2), scalp vein sets or IV cannula (2), disposable syringes – 5 ml with 24/25G IM needle (3 sets), adhesive tape and blank Case Reporting Formats (CRF).
- Outreach session sites should have an Anaphylaxis kit
- Contents of Anaphylaxis Kits
- All vaccinators must be trained to suspect signs and symptoms of anaphylaxis and to use the contents of the anaphylaxis kit to provide a single, age-appropriate dose of injection Adrenaline and arrange transportation of the patient to the nearest AEFI management centre/hospital for further treatment. This is crucial for saving lives in case of rare but life-threatening anaphylactic reactions.

  - Job aid for recognizing anaphylaxis
  - Dose chart for adrenaline as per age
  - 1 mL ampoule of adrenaline (1:1000 aqueous solution) - 3 nos.
  - Tuberculin syringes (1 mL) OR insulin syringe (of 40 units, without fixed needle) – 3 nos.
  - 24G/25G needles (1 inch) – 3 nos.
  - Swabs – 3 nos.
  - Updated contact information of DIO, Medical Officer(s) of PHC/CHC, referral center and local ambulance services
  - Certification by Medical Officer for expiry dates of contents



- Ensure that is enough stock / supply of injection adrenaline during the campaign, keeping in mind the short expiry period of the adrenaline.
- Each outreach session site should be linked to an identified AEFI management centre to provide immediate treatment for serious AEFI cases.
- Adequate transportation should be available to transfer persons with serious adverse reactions to nearest identified AEFI management centre or health facility. The vaccinators at the session sites must be aware of all relevant contact numbers like ambulance services (108 or 102), AEFI management centres, higher health care facilities, etc.

AEFI MANAGEMENT CENTRES

- States and UTs should identify **at least** one AEFI management centre in each block.
- During vaccination campaign, AEFI management centres must be identified near the vaccination sites. PHCs, CHCs, UPHCs, DHs or any other fixed health facilities with medical officers and paramedical staff should be identified as AEFI management centres. Private health facilities may also be made AEFI management centres.
- Every session site should be linked to a designated AEFI management centre. Contact details of medical officer, and address of AEFI management centre should be mentioned in the micro plans and should be known to staff of the session site.
- Adequate mobility support/ambulance services (102, 108) must be available to transport any person with AEFI from session sites to AEFI management centres.
- All MOs acting as supervisors will carry an AEFI management kit.
- All AEFI management centres should have an AEFI management kit and AEFI reporting forms.
- BMO and PHC MOIC should have mobility support to respond to AEFI investigation and management.
- AEFI management centres will report the AEFI as per laid out procedures in the national guidelines.
- If required, arrangements should be made to transfer the patient to a secondary or tertiary care hospital for specialist management.

Any adverse event following COVID-19 vaccination must be reported. There is no time limit (between vaccination and onset of symptoms) for reporting AEFIs. If the health worker or the treating physician or anyone suspects the event to be due to vaccination, it should be reported.

State and district authorities (DIO/CMO or the Block MO) should proactively reach out to all health care service providers such as medical colleges, hospitals (public, autonomous and private) and individual practitioners and sensitize them to report any adverse event following COVID-19 vaccine as per guidelines.

Doctors should ask and record history of COVID-19 vaccination in OPD prescriptions, casualty records, clinical treatment sheets, etc. Patients with history of COVID-19 vaccination (any duration) in which onset of symptoms has occurred AFTER COVID-19 vaccination should be considered as AEFIs and reported by the treating doctor to the nearest PHC doctor or District Immunization / RCH Officer in Case Reporting Format or telephonically. During investigations conducted by the DIO/district AEFI committee, all treatment records of the patient must be shared for causality assessment.

Professional bodies like IAP, IMA, IPHA, partner agencies like WHO-NPSP, UNICEF, UNDP, USAID, PATH and others should also be encouraged to support AEFI surveillance.

Blank copies of Case Reporting Formats (CRF) should be available with potential reporters to capture AEFI details. The reporter should also know whom to report and how to report. Thereafter, the case should be investigated by the district health authorities (DIO with support of the district AEFI committee members) as per national AEFI guidelines.

10.6.1 IMMEDIATE REPORTING OF SERIOUS AND SEVERE AEFIs

A serious or severe AEFI case needs to be reported immediately to the concerned Medical Officer or the appropriate health authorities. Soon after the identification / notification of a serious and severe AEFI, a two-step process must be initiated.

Report serious and severe AEFI to the appropriate authority (DIO or the nearest government health facility) in Case Reporting Format.

STEP 2

- Investigation of all reported serious and severe AEFI by District Immunization Officer or District AEFI Committee.
- All serious and severe AEFIs should be treated as a medical emergency and priority should be given to its management followed by its reporting and investigation on the standardized AEFI formats. All serious and severe AEFIs should be documented on a CASE REPORTING FORM (CRF).

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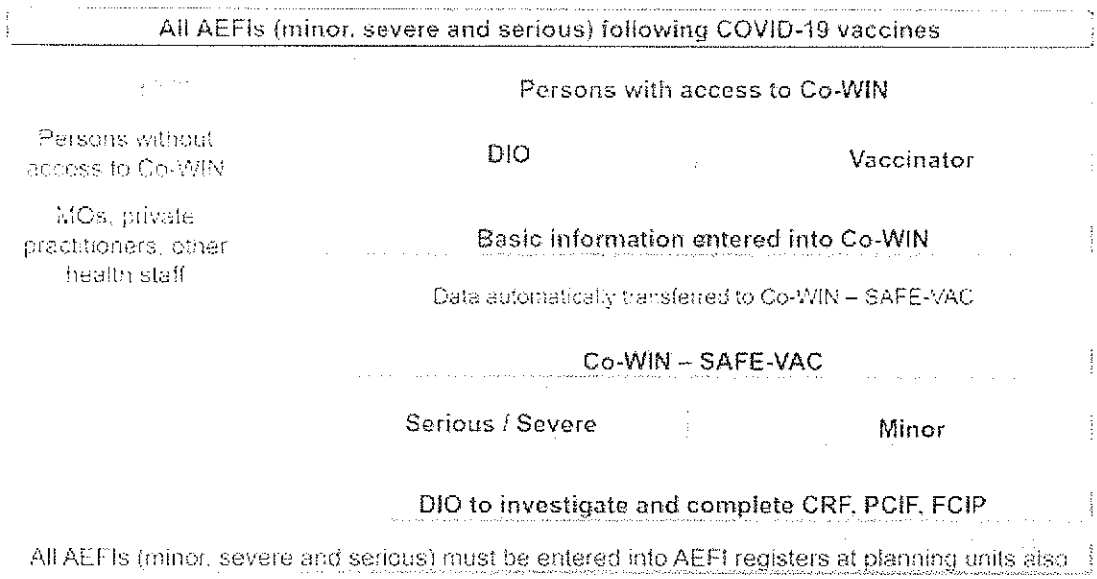
10.6.2 ROUTE OF REPORTING

Reporting through Co-WIN

Co-WIN is a web-based application developed for management of COVID-19 vaccination process including AEFI reporting. In the beneficiary module of Co-WIN, there is a provision for reporting of AEFI cases following COVID-19 vaccines.

- All adverse events (minor, severe and serious) following COVID-19 vaccination must be reported in Co-WIN by
  - The vaccinator through vaccinator's module
  - The DIO through district login in Co-WIN
- Immediately inform severe and serious AEFI cases telephonically by vaccinator to supervisor/medical officer/DIO.



- Only basic information is entered in Co-WIN, which is automatically transferred to SAFE-VAC.
- Once the basic case details are entered through Co-WIN, DIO can generate CRF for a serious / severe case. DIO, using a single sign-on through Co-WIN, can access SAFE-VAC for AEFIs related to COVID-19 vaccines and can enter information into CRF, PCIF, FCIF and can upload the documents

AEFI registers at PHC/block/planning unit levels: ANMs at block/planning unit should notify all AEFIs (serious, severe and minor) of their respective areas on weekly basis and document them in the AEFI register which is being maintained at the centre. Medical Officer In-charge of the block or planning unit (PHCs, CHCs etc.) should analyse the information regularly to look for any pattern or preventable programme errors and inform to District Immunization Officer.

Reporting and investigation of cluster AEFI cases: Cluster of AEFI cases is a specific condition which warrants immediate investigation because of its nature and seriousness. Each case of an AEFI cluster should be separately reported and investigated as per national AEFI guidelines.

For known anxiety clusters, separate CRFs should be filled for each case of a cluster. In confirmed anxiety clusters ONLY, if symptoms, clinical sequence of events, treatment and outcome are similar in all cases, a single, completely-filled PCIF and FCIF with all critical information recorded can be submitted. In addition, a summary report of the district AEFI committee certifying that this is an anxiety cluster should also be submitted along with the CRFs, PCIF, FCIF, hospital records, etc. of the cluster.

If cases of a cluster are showing different clinical pictures, separate PCIFs, FCIFs need to be filled for each case.

All serious and severe AEFI cases after COVID-19 vaccines must be investigated as per the National AEFI Guidelines. The process of investigation must be expedited in order to collect accurate and complete clinical and epidemiological facts so that causality assessment can be completed as soon as possible. Following actions are required in advance as preparation for investigation of cases:

- District AEFI committee meetings must be held at least one month prior to the start of COVID-19 vaccination. All members of the committee must be sensitized, and their services should be utilized, if needed, to investigate the cases.
- The district AEFI committees must include drug inspectors and ensure their support in the investigations.
- Medical Officers of government and private health care facilities, where serious AEFI cases are expected to reach for treatment, must be informed and sensitized about AEFI surveillance for immediate reporting and cooperation in investigations. Their support is also crucial for ensuring availability of medical records and clinical details of the cases which are required for causality assessment of the cases.

If a death following vaccination is reported, and the case was not hospitalised or clinical records are not available, relatives should be motivated to give consent for post mortem. Post mortems should be conducted to find the pathological cause of death. Any samples sent for laboratory tests should be followed up for obtaining results as soon as possible.

If consent for post mortem is refused, the AEFI verbal autopsy form should be administered as soon as possible.

The testing of vaccine samples is done very rarely. It should not be done unless there is a specific reason to doubt vaccine quality. Decision for testing will be taken by the district AEFI committee and the DIO should consult the state for this. Necessary guidelines and procedures for testing of COVID 19 vaccine samples available at that time should be followed.

Once investigations are complete for a serious/severe AEFI case and all supporting documents are available (hospital records, post mortem reports, final outcome), trained experts of the state and national AEFI committees assess the case as per globally accepted causality assessment protocol and available evidence of safety profile of the vaccine to classify it as follows:

WHO cause specific definition of AEFIs

1	2	3	4	5
Vaccine product-related reaction	Vaccine quality defect-related reaction	Immunization error-related reaction	Immunization anxiety-related reaction	Coincidental event
An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer	An AEFI that is caused by Inappropriate vaccine handling, prescribing or administration.	An AEFI arising from anxiety about the immunization.	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety

Training on AEFI surveillance will be a part of overall training package for COVID-19 vaccine implementation. Cascaded trainings will be conducted till the level of vaccinators. The content will provide information on AEFI surveillance system in the country with roles and responsibilities and specific information on AEFIs related to COVID-19 vaccines. All personnel involved in vaccination and AEFI surveillance including those in the private sector should be sensitized for identification and reporting of AEFIs.

8.1 ROLES AND RESPONSIBILITIES

Session site

Vaccinator Officer–vaccinator at the session site will be responsible for administering COVID19 vaccines safely as per guidelines and conveying appropriate messages to each beneficiary regarding management of AEFIs. S/he will also be responsible for reporting all AEFIs informed to her through recommended channels.

a. Inform the beneficiaries about the possible minor adverse events following COVID-19 vaccination

b. Ask beneficiaries to wait at vaccination sites for 30 minutes after vaccination

c. If any adverse event happens at the session site, manage appropriately

   i. Primary treatment to all AEFIs

   ii. Inj. Adrenaline for suspected anaphylaxis

   iii. Inform to MO / DIO

   iv. Arrange transport to refer, if required

   v. Enter the AEFI information in beneficiary module of Co-WIN

d. If any person reports about adverse event after 30 minutes following vaccination

   i. Ask beneficiary to contact nearest health care facility for prompt management

   ii. Enter the AEFI information in beneficiary module

Supervisor will ensure that the trained vaccinators at sessions are following all guidelines for safe administration of vaccines, conveying correct messages regarding adverse events and their management and ensure availability of anaphylaxis kits at the session site.

Medical Officer – The medical officer at the PHC will ensure that all session sites are tagged to an AEFI management centre with AEFI management kits. S/he should be trained in managing emergencies following COVID19 vaccination and ensures adrenaline ampoules at the session sites are within expiry dates.

a. DIO should ensure all health personnel involved in the COVID19 immunization programme are trained, cold chain is adequate, and processes are in place to manage AEFIs following vaccination.

b. DIO should network with all large hospitals and medical colleges (government, PSU, autonomous and private) and doctors to report minor, serious and severe AEFIs using the recommended processes.

c. District AEFI Committee - DIO will expand the committee to include neurologists, cardiologists, respiratory medicine specialists/medical specialists and obstetrician & gynaecologist. These specialists will support DIOs in investigation of the case and establishing a diagnosis for causality assessment. District AEFI committee shall meet at least 15 days before the campaign to familiarise itself regarding preparations for vaccination, potential vaccine issues, is available to conduct urgent serious AEFI investigations and assesses investigation reports to give probable diagnosis.

d. If any serious/severe AEFI case is reported

- Arrange for clinical management at secondary or tertiary care hospitals
- Investigate the case
- If the case information has not already been entered in Co-WIN by vaccinator, enter the basic information through district log-in (information is automatically transferred from Co-WIN to SAFE-VAC)
- Complete CRF, PCIF and FCIF in SAFE-VAC
- Entry of all AEFIs (minor, severe and serious) reported directly to DIO by persons not having access to Co-WIN (MOs, private practitioners, other healthcare staff etc.)

Preparatory	• Expansion of District AEFI Committee • Sensitization of District AEFI Committee members • Expansion of reporting network – medical colleges, private practitioners
AEFI Management	• Arrange for clinical management • Investigate the case • Enter the basic information into Co-WIN • Complete CRF, PCIF and FCIF in SAFE-VAC
Reporting	• Entry of all AEFIs (minor, severe and serious) reported directly to DIO by persons not having access to Co-WIN (MOs, private practitioners, other healthcare staff etc.)

- **SEPIO**–Ensure all districts are using trained vaccinators for session sites, and they are aware of procedures for managing, reporting and investigating AEFIs as per guidelines. He/she ensures state AEFI committee and district AEFI committee members are oriented on COVID19 vaccination and are aware of their roles and responsibilities.
- **State AEFI Committee**–SEPIO will expand State AEFI Committee to include neurologists, cardiologists, respiratory medicine specialists/medical specialists and obstetrician & gynaecologist. State AEFI committee meets at least 7 days before the campaign to familiarise itself regarding preparations for vaccination, potential vaccine issues, be available to conduct urgent serious AEFI investigations and assess causality of AEFI cases following COVID19 vaccinations within recommended timelines.

a. **MOHFW (including AEFI Secretariat)** – Coordinates with partners to ensure preparations are in place for COVID 19 vaccination. Reported and investigated AEFIs are causally assessed and database analysed for potential signals. Consultative meetings with experts are held for further management of potential signals.

b. **National AEFI Committee** – National AEFI Committee will be expanded to include neurologists, cardiologists, respiratory medicine specialists/medical specialists and obstetrician & gynaecologist. The national AEFI committee monitors the progress and analysis/ assessment of AEFIs reported and investigated in the districts, conducts and approves causality assessment results, assesses causality assessment data and active surveillance data for better understanding of the safety profile of COVID19 vaccines.

ADVERSE EVENTS OF SPECIAL INTEREST (AESI) SURVEILLANCE FOR COVID 19

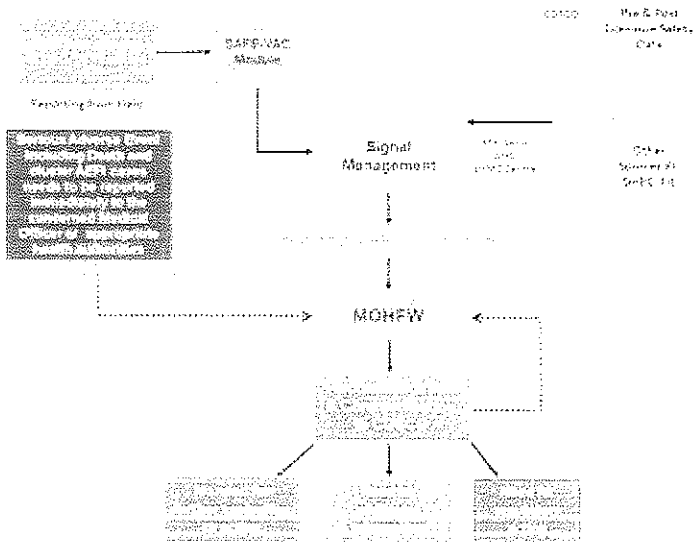
When a new vaccine is approved for use, there is a theoretical possibility of occurrence of some events based on available data for existing and new vaccines. Such Adverse Events of Special Interest (AESI) should be monitored

- To ensure these are not occurring at a rate more than the background or expected rate and
- To elicit safety issues related to these as early as possible and take appropriate action

An active AESI sentinel surveillance, which is one of the ways to assess these AESIs, will complement the regular passive AEFI surveillance system. The combined evidences from routine AEFI surveillance and active AESI surveillance will further help in generating sound evidence to characterize the safety profile of the new vaccine. A few sentinel sites across the country will be chosen for this AESI surveillance as part of separate project.

SIGNAL MANAGEMENT AND SAFETY MONITORING

The evaluation of safety signals identified through reported AEFIs is part of vaccine vigilance and is essential to ensure that regulatory authorities and immunization programme have the most up-to-date information on benefits and risks. Database of AEFI cases reported from the districts, can be analysed for safety signals by integrating automated data-mining and appropriate statistical methodologies. The evidences generated by the system will equip decision makers to take important decisions to ensure vaccines administered under the programme are safe.



1. Expand committees at various levels to include neurologists, cardiologists, respiratory medicine specialists/medical specialists and obstetrician & gynaecologist
2. Expand reporting network through sensitizing medical colleges, private practitioners and medical officers
3. Expedite investigation and causality assessment of cases
4. Prompt case management / referral of AEFI cases
5. Vaccinators at the session sites and DIOs at district level can directly enter basic information of AEFIs following COVID-19 vaccines, which will be transferred automatically to SAFE-VAC for further processing.

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Annexure - A14

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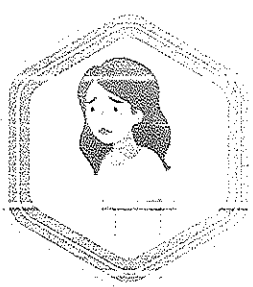
कोविड-19 का टीका पूरी तरह सुरक्षित और प्रभावी है

टीकाकरण के पश्चात सामान्य प्रतिकूल प्रभाव बहुत हल्के होते हैं।

टीके वाले स्थान पर हल्के लाल निशान

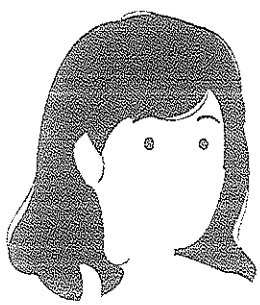
बुखार

सरदर्द



थकान

यदि कोई अन्य प्रतिक्रिया हो तो, अपने आप अथवा पैरासिटामोल की गोली लेने से ठीक हो जाए।
यदि ठीक न हो तो, अपने पास के अस्पताल में संपर्क करें।



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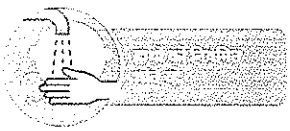
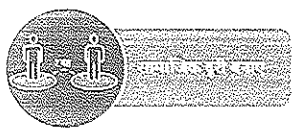
टीकाकरण के पश्चात किसी भी अप्रिय घटना की सूचना
रजिस्टर्ड मोबाइल नंबर से www.cowin.gov.in पर भी दी जा सकती है ।

कोविड अनरूप व्यवहारों का प्रयोग करते रहें।





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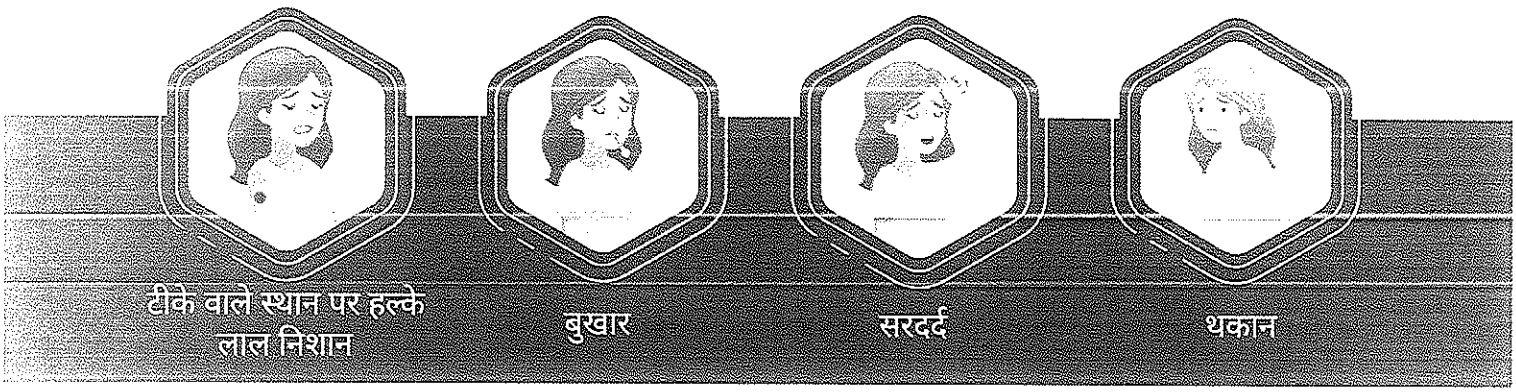
कोविड-19 का टीका पूरी तरह सुरक्षित और प्रभावी है

टीकाकरण के पश्चात सामान्य प्रतिकूल प्रभाव बहुत हल्के होते हैं।

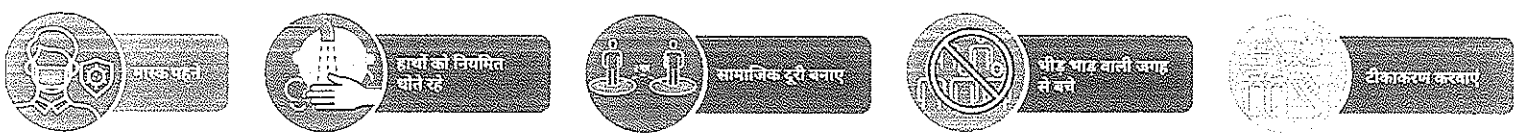


कोविड-19 टीकाकरण के पश्चात गंभीर प्रतिकूल परिणाम जैसे अस्पताल में भर्ती होना और मृत्यु की संभावना बहुत कम है।

प्रिय डॉक्टर,

टीकाकरण के पश्चात किसी भी अप्रिय घटना की सूचना रजिस्टर्ड मोबाइल नंबर से www.cowin.gov.in पर भी दी जा सकती है।

कोविड अनरूप व्यवहारों का प्रयोग करते रहें।



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टीकाकरण के पश्चात निम्नलिखित

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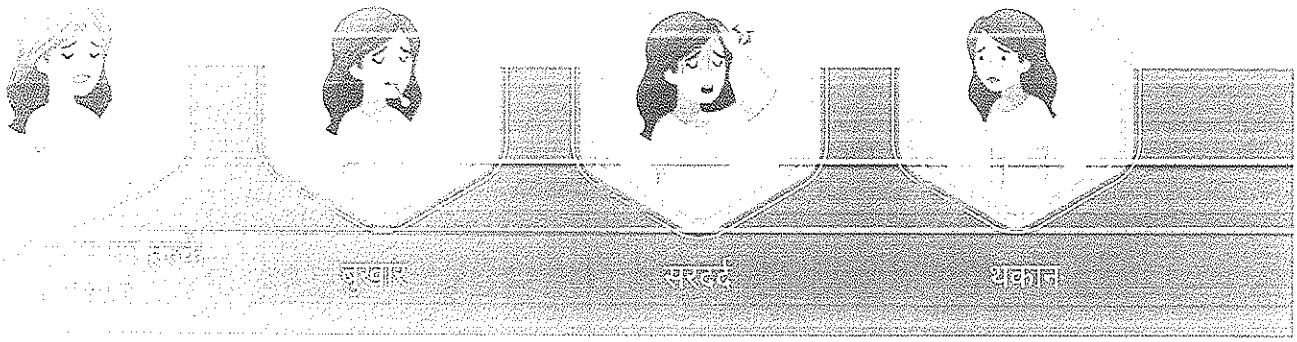
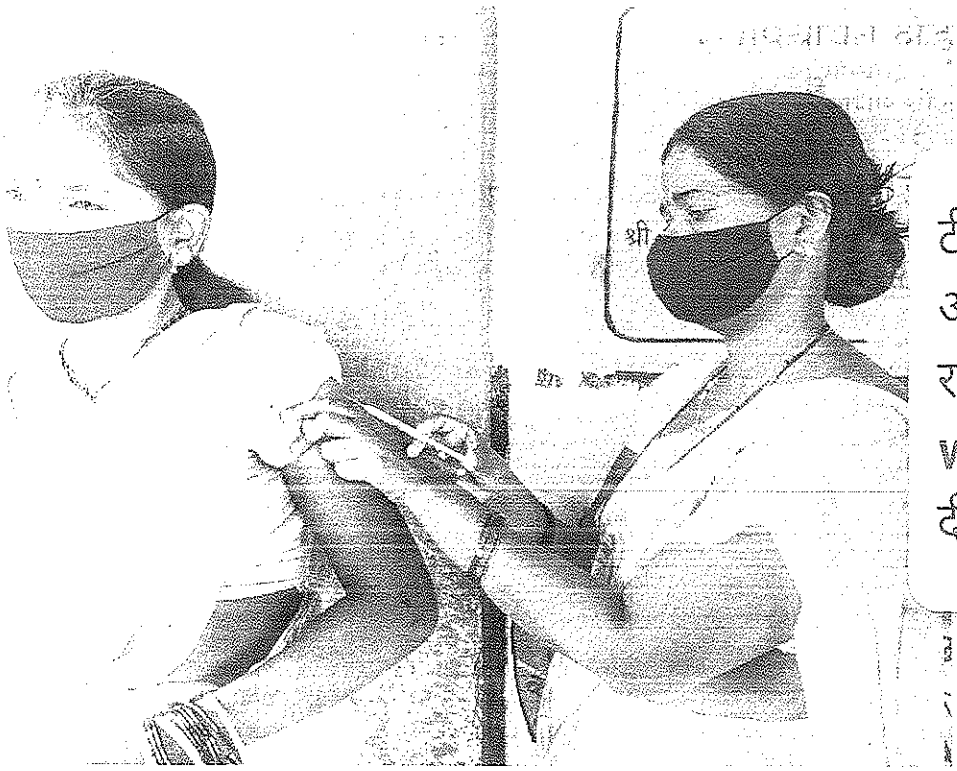


कोविड-19 टीकाकरण के पश्चात गंभीर प्रतिकूल परिणाम जैसे अस्पताल में भर्ती होना और मृत्यु की संभावना बहुत कम है।



टीकाकरण के पश्चात किसी भी अप्रिय घटना की सूचना रजिस्टर्ड मोबाइल नंबर से **www.cowin.gov.in** पर भी दी जा सकती है।

कोविड अनरूप व्यवहारों का प्रयोग करते रहें।

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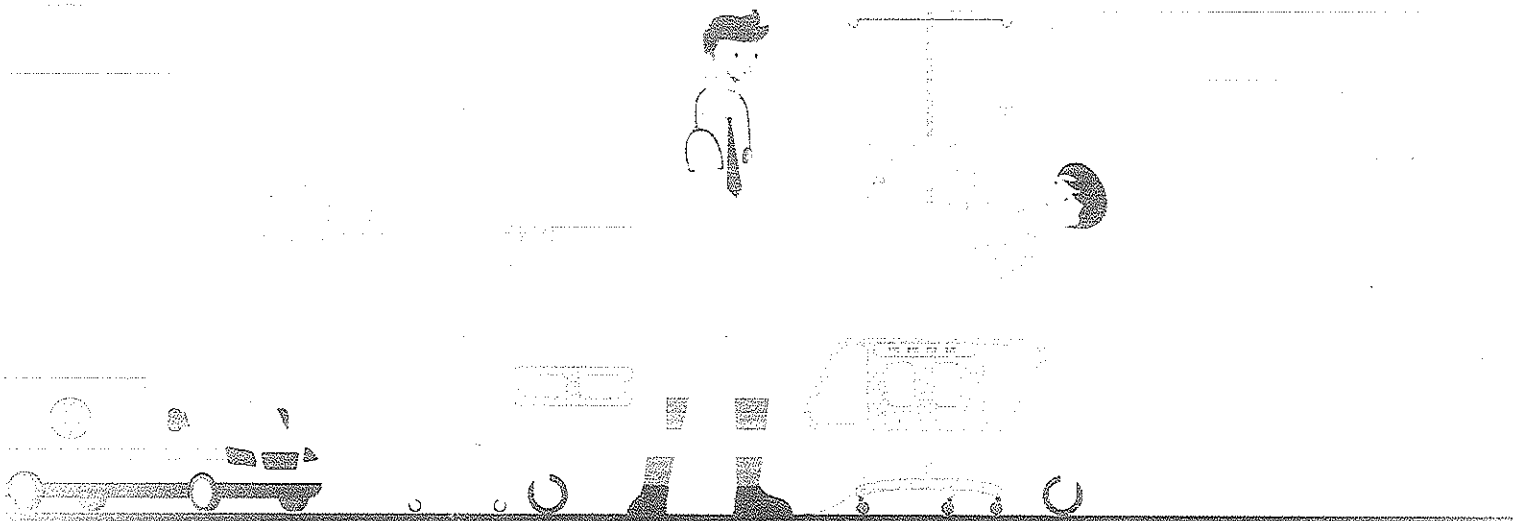

कोविड-19 टीकाकरण के पश्चात गंभीर प्रतिकूल परिणाम जैसे अस्पताल में भर्ती होना और मृत्यु की संभावना बहुत कम है।

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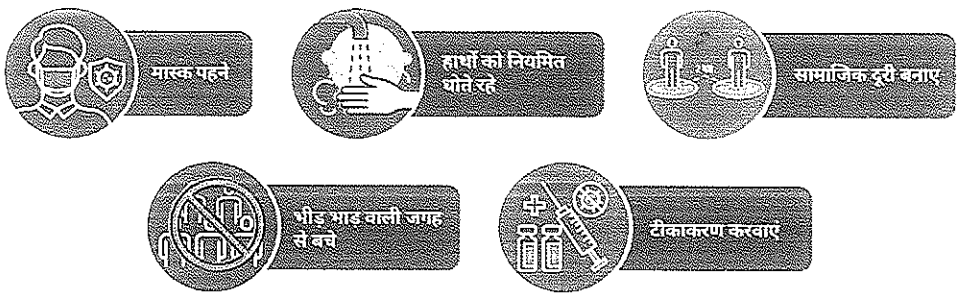
कोविड अनरूप व्यवहारों का प्रयोग करते रहें।



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स्वास्थ्य एवं परिवार कल्याण मंत्रालय
भारत सरकार

Help us to help you

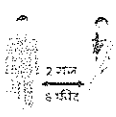
आम तौर पर वैक्सीन सुरक्षित होती है।

आपको वैक्सीन लगवाने के बाद 2-3 दिन तक इंजेक्शन की जगह पर दर्द, लालीपन और सूजन, हल्का बुखार, सर में दर्द, कमजोरी जैसी तकलीफे हो सकती है। ये सामान्य प्रभाव है एवं अपने आप ठीक हो जाते है या आपको पेरासिटामोल गोली लेनी पड़ सकती है।

यदि लक्षण बने रहते हैं, तो आप सलाह के लिए हेल्पलाइन नंबर 1075 पर कॉल कर सकते हैं या चिकित्सा सलाह और उपचार के लिए नज़दीकी सरकारी स्वास्थ्य सुविधा केन्द्र पर जा सकते हैं।

कृपया टीकाकरण टीम को सूचित करें जिससे आपकी परेशानी को Co-WIN पोर्टल पर भी रिकार्ड किया जा सके।

कोविड अनुरूप व्यवहार का पालन करें



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Vaccines are generally safe

You may have pain, redness and swelling at the injection site, low grade fever, headache, generalised weakness, discomfort, etc. for two or three days after vaccination. These are normal and expected reactions which get better on their own or can be relieved using paracetamol tablets

If symptoms persist, you may call at the helpline number 1075 for guidance or visit the nearest government health facility for medical advice and treatment

The vaccination team may also be informed about the adverse event for further reporting into the Co-WIN portal

Follow COVID appropriate behaviour

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Help us to help you

OVID-19 vaccines are safe and effective

Common side effects of COVID-19 vaccines are mild

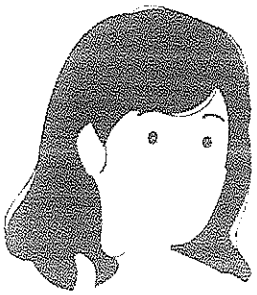
oreness or redness at injection site

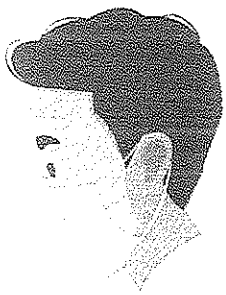
Fever

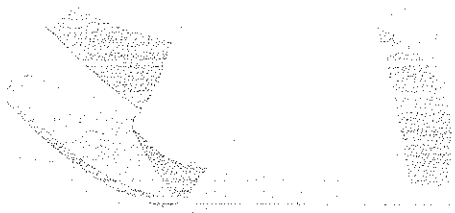
Headache

Fatigue

e normal and get better on their own or can be relieved using paracetamol
If symptoms persist, please visit your nearest healthcare facility

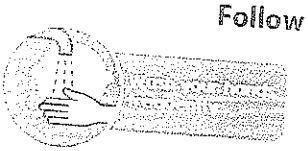


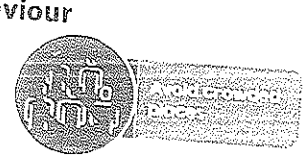




Report any side effect at www.cowin.gov.in
using your registered mobile number

Follow COVID appropriate behaviour





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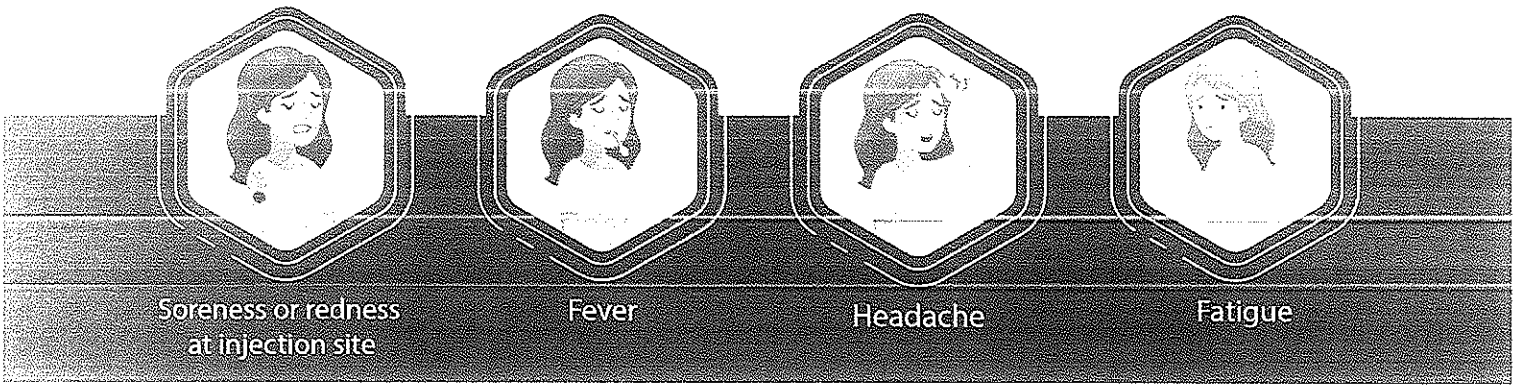
COVID-19 vaccines are safe and effective

Common side effects of COVID-19 vaccines are mild and include

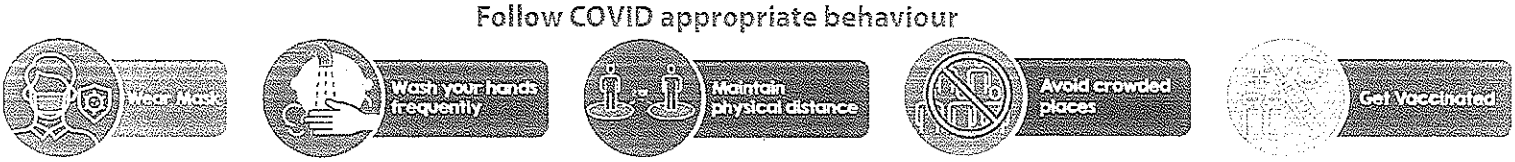


Serious side effects leading to hospitalization or deaths following COVID-19 vaccination are very rare

Dear Doctor,

You can report side effects following the COVID-19 vaccination of a person by using their registered mobile number at www.cowin.gov.in

Follow COVID appropriate behaviour



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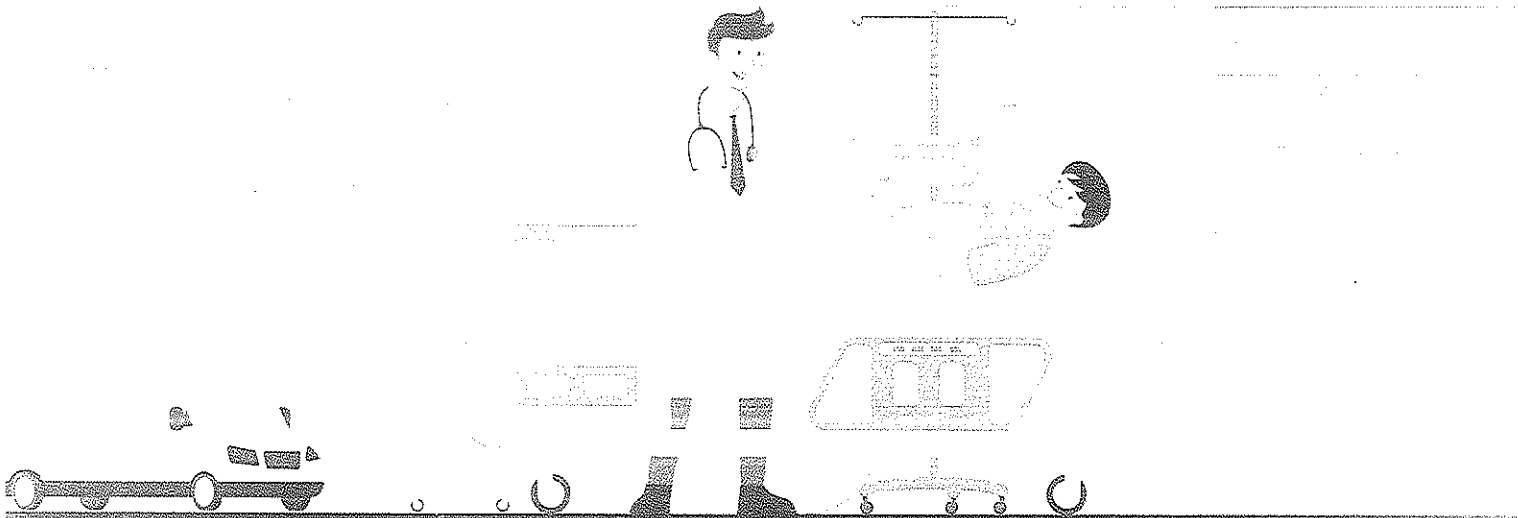
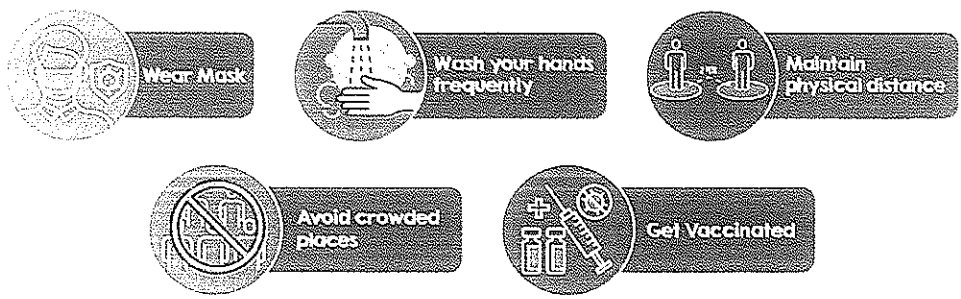


Serious adverse events leading to hospitalization or death following COVID-19 vaccination are very rare

www.cowin.gov.in

Follow COVID appropriate behaviour



mohfw.gov.in @MoHFWIndia @MoHFW_INDIA @mohfwindia mohfwindia

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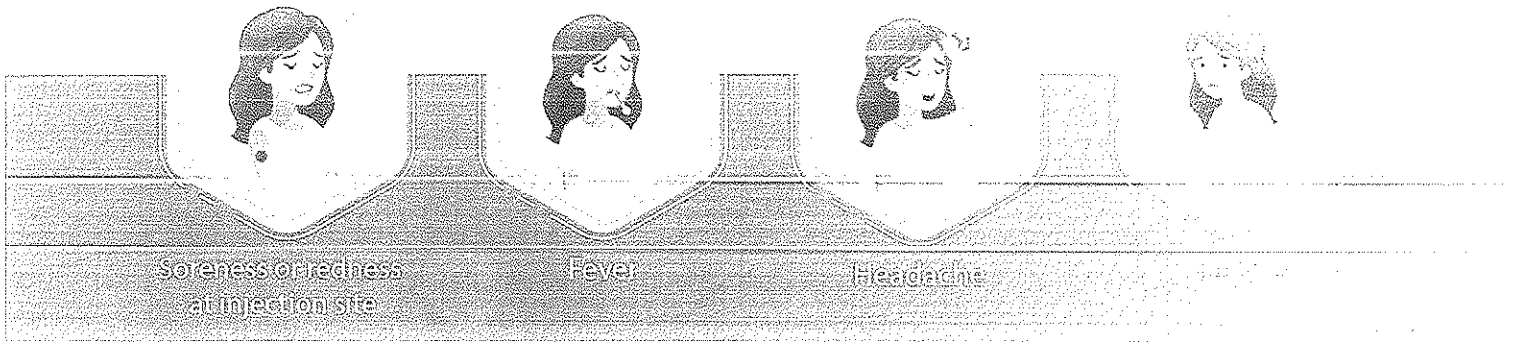
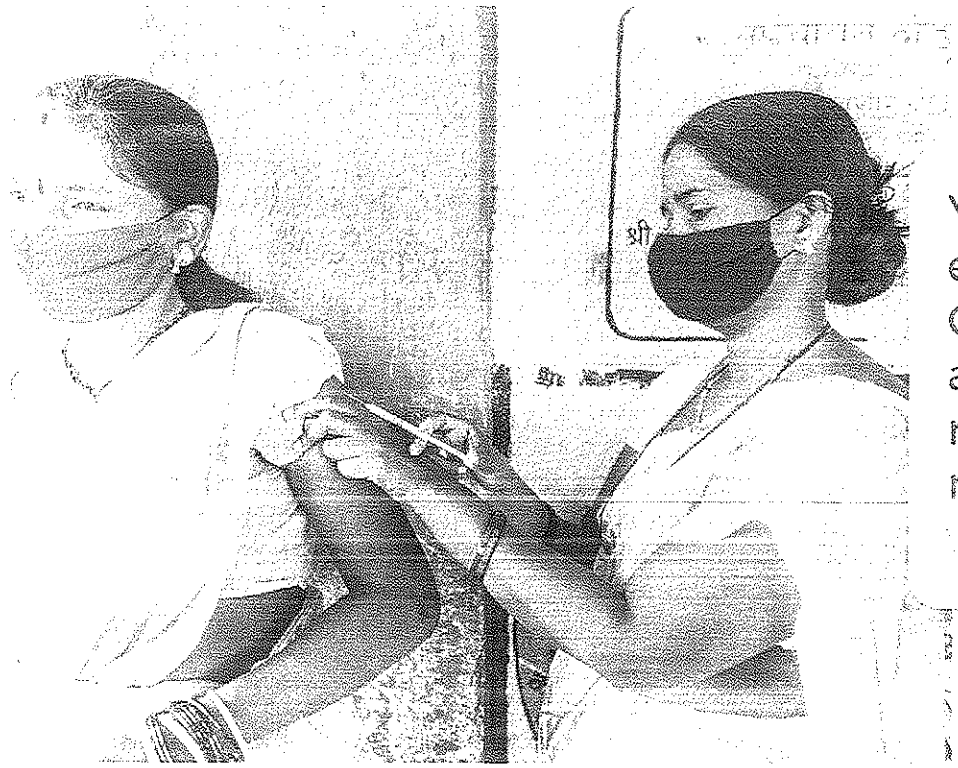
Ministry of Health & Family Welfare
Government of India

Help us to help you

Common COVID-19 vaccine side effects are:



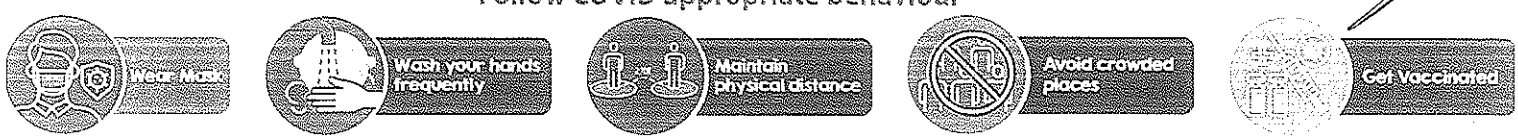
Serious side effects leading to hospitalization or deaths following COVID-19 vaccination are very rare



You can report side effects following the COVID-19 vaccination of a person by using their registered mobile number at

True Copy

Follow COVID appropriate behaviour



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Annexure-A15

Z-16025/05/2012 Imm p/f
Government of India
Ministry of Health & Family Welfare
Immunization Division

Nirman Bhawan, New Delhi
Date: 07th December 2021

Causality assessment results of 178 reported Serious Adverse Events Following Immunization (AEFI) cases following COVID-19 vaccination approved by National AEFI Committee on 22nd November 2021.

The Immunization Division, MoHFW has taken several steps to strengthen the national AEFI surveillance system for COVID-19 vaccinations. Considering the importance and critical nature of the task, steps were taken to include medical specialists, cardiologists, neurologists, pulmonary medicine specialists, obstetrician-gynecologist as members of the causality assessment sub-committee at the national level. A Special Group has been framed to conduct causality assessment of AEFIs following COVID-19 vaccination. The results of causality assessment done by this Special Group is discussed in the national AEFI committee meeting for final approval.

The results of the causality assessment for 178 cases completed on 22nd November 2021 after thorough review, deliberation and approval by the National AEFI Committee is given in the annexure (anonymized line list of the causality assessment done by the National AEFI Committee).

67 out of 178 cases for which Causality assessment has been done were found to have **consistent causal association to vaccination.** Of these 67 cases, 52 cases were vaccine product related reaction including 04 deaths and 15 cases were immunization anxiety related reaction. 77 cases have inconsistent causal association to vaccination (**coincidental - not linked to vaccination**), including 33 death cases. 30 cases were in indeterminate category including 03 death cases. There were 04 cases in unclassifiable category, including 03 death cases.

Vaccine product related reactions are expected reactions that can be attributed to vaccination based on current scientific evidence. Examples of such reactions are allergic reactions and anaphylaxis, etc.

Indeterminate reactions are reactions which have occurred soon after vaccination but there is no definitive evidence in current literature or clinical trial data that this event could have been caused due to the vaccine. Further observations, analysis and studies are required.

Unclassifiable events are events which have been investigated but there is not enough evidence for assigning a diagnosis due to missing crucial information. When this relevant information becomes available, the case may be reconsidered for causality assessment.

Coincidental events are events that are reported following immunization but for which a clear cause other than vaccination is found on investigation.

Overall, the benefits of vaccination are overwhelmingly greater than the small risk of harm. However, as a measure of utmost precaution, all emerging signals of harm are being constantly tracked and reviewed periodically.

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CAUSALITY CLASSIFICATION OF 178 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 22 NOV 2021- (NEW DELHI)

A1 - VACCINE PRODUCT RELATED REACTION

A2 - VACCINE QUALITY DEFECT RELATED REACTION

A3 - IMMUNIZATION ERROR RELATED REACTION

A4 - IMMUNIZATION ANXIETY RELATED REACTION

B1 - TEMPORAL RELATIONSHIP IS CONSISTENT BUT THERE IS INSUFFICIENT DEFINITIVE EVIDENCE FOR VACCINE CAUSING EVENT

B2 - REVIEWING FACTORS RESULT IN CONFLICTING TRENDS OF CONSISTENCY AND INCONSISTENCY WITH CAUSAL ASSOCIATION TO IMMUNIZATION

C - COINCIDENTAL - UNDERLYING OR EMERGING CONDITION(S), OR CONDITIONS CAUSED BY EXPOSURE TO SOMETHING OTHER THAN VACCINE

D - UNCLASSIFIABLE

S. NO.	NATIONAL ID	YEAR	AGE (IN YEARS)	SEX	REASON FOR REPORTING/ OUTCOME	DATE OF VACCINATION (DD/MM/YYYY)	VACCINE	DIAGNOSIS	CLASSIFICATION* BY NATIONAL AEFI COMMITTEE	DATE OF APPROVAL BY NATIONAL AEFI COMMITTEE
1	IND(CO-AEFI)CGMMD21002	2021	44	FEMALE	HOSPITALIZED & RECOVERED	30-01-2021	COVISHIELD	ACUTE TRANSVERSE MYELITIS	B1	22-Nov-21
2	IND(CO-AEFI)HAJND21001	2021	35	FEMALE	SEVERE & RECOVERED	23-01-2021	COVISHIELD	FACIAL PALSY	B1	22-Nov-21
3	IND(CO-AEFI)KASHI21002	2021	35	FEMALE	HOSPITALIZED & RECOVERED	25-01-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
4	IND(CO-AEFI)KAGBG21001	2021	23	FEMALE	HOSPITALIZED & RECOVERED	05-02-2021	COVISHIELD	SEIZURE (KNOWN PATIENT OF SEIZURES AND WAS ON TAPERING DOSE OF PHENYTOIN)	C	22-Nov-21
5	IND(CO-AEFI)MPSVP21001	2021	23	FEMALE	HOSPITALIZED & RECOVERED	27-01-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
6	IND(CO-AEFI)MHBMC21009	2021	42	FEMALE	HOSPITALIZED & RECOVERED	25-01-2021	COVISHIELD	COVID INFECTION	C	22-Nov-21
7	IND(CO-AEFI)PDPNY21001	2021	47	FEMALE	HOSPITALIZED & RECOVERED	09-02-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
8	IND(CO-AEFI)PBSAN21007	2021	33	MALE	HOSPITALIZED & RECOVERED	16-01-2021	COVISHIELD	FEVER	A1	22-Nov-21
9	IND(CO-AEFI)SIEST21003	2021	29	FEMALE	HOSPITALIZED & RECOVERED	19-01-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
10	IND(CO-AEFI)UAHRD21001	2021	32	FEMALE	HOSPITALIZED & RECOVERED	16-01-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
11	IND(CO-AEFI)WBRMH21002	2021	37	MALE	SEVERE & RECOVERED	22-01-2021	COVISHIELD	FEVER	A1	22-Nov-21
12	IND(CO-AEFI)WBHGL21001	2021	48	FEMALE	HOSPITALIZED & RECOVERED	17-02-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
13	IND(CO-AEFI)TSMBR21001	2021	36	FEMALE	HOSPITALIZED & RECOVERED	16-02-2021	COVISHIELD	ACUTE ISCHAEMIC THROMBOEMBOLIC INFARCT IN A KNOWN CASE OF DIABETES MELLITUS AND RHEUMATIC HEART DISEASE	C	22-Nov-21
14	IND(CO-AEFI)KEKNU21001	2021	24	FEMALE	DEATH	03-02-2021	COVISHIELD	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME LIKE ILLNESS WITH COVID 19 INFECTION	B2	22-Nov-21
15	IND(CO-AEFI)WBCAL21017	2021	43	MALE	HOSPITALIZED & RECOVERED	13-02-2021	COVISHIELD	VASOVAGAL SYNCOPE	A4	22-Nov-21
16	IND(CO-AEFI)MHBMC21016	2021	55	MALE	HOSPITALIZED & RECOVERED	19-02-2021	COVISHIELD	ISCHAEMIC HEART DISEASE WITH PREVIOUS HISTORY OF SIMILAR EPISODE	C	22-Nov-21
17	IND(CO-AEFI)MHBMC21018	2021	58	MALE	HOSPITALIZED & RECOVERED	28-01-2021	COVISHIELD	FACIAL PALSY	B1	22-Nov-21
18	IND(CO-AEFI)MHBMC21019	2021	27	FEMALE	HOSPITALIZED & RECOVERED	20-02-2021	COVISHIELD	ALLERGIC RASH WITH FEVER	A1	22-Nov-21
19	IND(CO-AEFI)ORGJM21002	2021	56	FEMALE	HOSPITALIZED & RECOVERED	25-02-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
20	IND(CO-AEFI)KEWYD21002	2021	39	FEMALE	SEVERE & RECOVERED	29-01-2021	COVISHIELD	FACIAL PALSY	B1	22-Nov-21
21	IND(CO-AEFI)ORSUN21003	2021	24	FEMALE	HOSPITALIZED & RECOVERED	18-01-2021	COVISHIELD	FEVER, BODYACHE, VOMITTING, FATIGUE AND VERTIGO	A1	22-Nov-21
22	IND(CO-AEFI)UPBRP21001	2021	71	MALE	HOSPITALIZED & RECOVERED	04-03-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
23	IND(CO-AEFI)MHBMC21022	2021	51	MALE	SEVERE & RECOVERED	22-02-2021	COVISHIELD	LEFT 3RD NERVE PALSY (PUPIL SPARING) INCOMPLETE	C	22-Nov-21
24	IND(CO-AEFI)MHBMC21001	2021	39	FEMALE	HOSPITALIZED & RECOVERED	22-01-2021	COVISHIELD	FEVER WITH GENERALISED WEAKNESS	A1	22-Nov-21
25	IND(CO-AEFI)ORNUP21002	2021	26	FEMALE	HOSPITALIZED & RECOVERED	23-01-2021	COVISHIELD	FEVER WITH HEADACHE	A1	22-Nov-21
26	IND(CO-AEFI)ORKRD21002	2021	52	FEMALE	HOSPITALIZED & RECOVERED	21-01-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
27	IND(CO-AEFI)GURJT21003	2021	25	FEMALE	HOSPITALIZED & RECOVERED	28-01-2021	COVISHIELD	SEIZURE	D	22-Nov-21
28	IND(CO-AEFI)TRTRW21005	2021	46	FEMALE	HOSPITALIZED & RECOVERED	04-02-2021	COVISHIELD	FEVER	A1	22-Nov-21
29	IND(CO-AEFI)MHBMC21002	2021	47	FEMALE	HOSPITALIZED & RECOVERED	25-01-2021	COVISHIELD	FEVER, MALAISE & VOMITTING	A1	22-Nov-21
30	IND(CO-AEFI)GUBVN21001	2021	35	FEMALE	SEVERE & RECOVERED	19-01-2021	COVISHIELD	FEVER	A1	22-Nov-21
31	IND(CO-AEFI)HPHMR21001	2021	56	FEMALE	DEATH	29-01-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B2	22-Nov-21
32	IND(CO-AEFI)UPSHP21001	2021	28	MALE	HOSPITALIZED & RECOVERED	04-02-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
33	IND(CO-AEFI)APPKM21001	2021	24	FEMALE	HOSPITALIZED & RECOVERED	23-01-2021	COVISHIELD	SEPSIS WITH PYELONEPHRITIS WITH ACUTE KIDNEY INJURY	C	22-Nov-21
34	IND(CO-AEFI)TRTRW21006	2021	25	MALE	HOSPITALIZED & RECOVERED	11-02-2021	COVISHIELD	ENCEPHALOMALACIA WITH GLIOSIS	C	22-Nov-21
35	IND(CO-AEFI)TSMDK21001	2021	42	FEMALE	HOSPITALIZED & RECOVERED	19-01-2021	COVISHIELD	SEIZURE DISORDER	C	22-Nov-21
36	IND(CO-AEFI)WBCAL21007	2021	51	FEMALE	HOSPITALIZED & RECOVERED	16-01-2021	COVISHIELD	ACUTE FEBRILE ILLNESS	A1	22-Nov-21
37	IND(CO-AEFI)WBCAL21010	2021	40	MALE	SEVERE & RECOVERED	19-01-2021	COVISHIELD	FEVER WITH ARTHRALGIA	A1	22-Nov-21
38	IND(CO-AEFI)KAUDU21002	2021	52	MALE	HOSPITALIZED & RECOVERED	09-02-2021	COVISHIELD	VIRAL PNEUMONIA	C	22-Nov-21
39	IND(CO-AEFI)WBCAL21011	2021	49	MALE	SEVERE & RECOVERED	29-01-2021	COVISHIELD	FACIAL PALSY	B1	22-Nov-21

CAUSALITY CLASSIFICATION OF 178 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 22 NOV 2021- (NEW DELHI)

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S. NO.	NATIONAL ID	YEAR	AGE (IN YEARS)	SEX	REASON FOR REPORTING/ OUTCOME	DATE OF VACCINATION (DD/MM/YYYY)	VACCINE	DIAGNOSIS	CLASSIFICATION* BY NATIONAL AEFI COMMITTEE	DATE OF APPROVAL BY NATIONAL AEFI COMMITTEE
40	IND(CO-AEFI)HAPKL21001	2021	46	FEMALE	SEVERE & RECOVERED	25-01-2021	COVISHIELD	BILATERAL CENTRAL RETINAL VEIN OCCLUSION	B1	22-Nov-21
41	IND(CO-AEFI)HAPKL21002	2021	37	MALE	SEVERE & RECOVERED	05-02-2021	COVISHIELD	UNCONTROLLED DIABETES WITH ANTERIOR UVEITIS AND RETINOPATHY	C	22-Nov-21
42	IND(CO-AEFI)KADHA21002	2021	40	FEMALE	HOSPITALIZED & RECOVERED	10-02-2021	COVISHIELD	BILATERAL PNEUMONIA WITH DIABETES MELLITUS	C	22-Nov-21
43	IND(CO-AEFI)KAMYS21003	2021	41	MALE	HOSPITALIZED & RECOVERED	12-02-2021	COVISHIELD	DIABETIC KETOACIDOSIS WITH HYPOTHYROIDISM WITH FOCAL SEIZURE	C	22-Nov-21
44	IND(CO-AEFI)WBMBD21003	2021	40	FEMALE	SEVERE & RECOVERED	25-01-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
45	IND(CO-AEFI)DLWES21007	2021	27	MALE	HOSPITALIZED & RECOVERED	23-02-2021	COVISHIELD	BRONCHIAL ASTHMA WITH ACUTE EXACERBATION	C	22-Nov-21
46	IND(CO-AEFI)UPBRL21004	2021	31	FEMALE	SEVERE & RECOVERED	29-01-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
47	IND(CO-AEFI)CGBTR21001	2021	23	FEMALE	HOSPITALIZED & RECOVERED	04-02-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
48	IND(CO-AEFI)KEKZK21003	2021	62	FEMALE	HOSPITALIZED & RECOVERED	02-02-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
49	IND(CO-AEFI)HAFBD21001	2021	77	FEMALE	DEATH	06-03-2021	COVISHIELD	ACUTE CORONARY SYNDROME IN A KNOWN CASE OF DIABETES MELLITUS	C	22-Nov-21
50	IND(CO-AEFI)MHBMC21027	2021	87	MALE	HOSPITALIZED & RECOVERED	11-02-2021	COVISHIELD	COVID-19 DISEASE	C	22-Nov-21
51	IND(CO-AEFI)MHBMC21026	2021	77	MALE	HOSPITALIZED & RECOVERED	04-03-2021	COVISHIELD	CEREBROVASCULAR ACCIDENT WITH DIABETES MELLITUS	C	22-Nov-21
52	IND(CO-AEFI)TNVPM21001	2021	76	FEMALE	DEATH	06-03-2021	COVISHIELD	ACUTE GASTROENTERITIS WITH HYPOGLYCAEMIA, WITH DYSELECTROLAEMIA, WITH METABOLIC ENCEPHALOPATHY WITH ATRIAL FIBRILATION	C	22-Nov-21
53	IND(CO-AEFI)BICPW21003	2021	74	FEMALE	DEATH	08-03-2021	COVISHIELD	ACUTE CORONARY SYNDROME WITH DIABETES MELLITUS, HYPERTENSION AND ASTHMA	C	22-Nov-21
54	IND(CO-AEFI)WBMBD21008	2021	63	MALE	HOSPITALIZED & RECOVERED	10-03-2021	COVISHIELD	HEMOPTYSIS	C	22-Nov-21
55	IND(CO-AEFI)BIAGB21001	2021	45	FEMALE	DEATH	08-03-2021	COVISHIELD	SUDDEN UNEXPLAINED DEATH	D	22-Nov-21
56	IND(CO-AEFI)SIEST21001	2021	36	FEMALE	HOSPITALIZED & RECOVERED	20-01-2021	COVISHIELD	ACUTE FEBRILE ILLNESS WITH HEADACHE AND MYALGIA	A1	22-Nov-21
57	IND(CO-AEFI)WBDJL21007	2021	22	MALE	SEVERE & RECOVERED	29-01-2021	COVISHIELD	CHILLS WITH NAUSEA	A1	22-Nov-21
58	IND(CO-AEFI)APPKM21003	2021	39	FEMALE	DEATH	21-01-2021	COVISHIELD	MULTIPLE MYELOMA, SEPSIS, ACUTE ON CHRONIC KIDNEY DISEASE	C	22-Nov-21
59	IND(CO-AEFI)WBSPG21010	2021	77	MALE	DEATH	09-03-2021	COVISHIELD	UNEXPLAINED DEATH	D	22-Nov-21
60	IND(CO-AEFI)APEGV21002	2021	87	MALE	DEATH	15-03-2021	COVISHIELD	SUDDEN CARDIAC DEATH WITH DIABETES MELLITUS	C	22-Nov-21
61	IND(CO-AEFI)GUGIR21001	2021	40	FEMALE	HOSPITALIZED & RECOVERED	25-02-2021	COVISHIELD	SEIZURE DISORDER	C	22-Nov-21
62	IND(CO-AEFI)HPMND21002	2021	69	MALE	HOSPITALIZED & RECOVERED	09-03-2021	COVISHIELD	MODERATE COVID 19 DISEASE	C	22-Nov-21
63	IND(CO-AEFI)JHRNC21005	2021	35	MALE	HOSPITALIZED & RECOVERED	10-03-2021	COVISHIELD	ACUTE INFERO POSTERIOR WALL MYOCARDIAL INFARCTION	B1	22-Nov-21
64	IND(CO-AEFI)SISTH21001	2021	64	FEMALE	DEATH	03-03-2021	COVISHIELD	HYPERTENSION WITH COPD WITH ACUTE EXACERBATION WITH LOWER RESPIRATORY TRACT INFECTION WITH RESPIRATORY FAILURE	C	22-Nov-21
65	IND(CO-AEFI)GOGOS21002	2021	39	FEMALE	SEVERE & RECOVERED	02-02-2021	COVISHIELD	FEVER WITH LOCAL SITE PAIN	A1	22-Nov-21
66	IND(CO-AEFI)APPKM21004	2021	78	MALE	DEATH	08-03-2021	COVISHIELD	CORONARY ARTERY DISEASE WITH ANTERIOR WALL MYOCARDIAL INFARCTION WITH TYPE 2 DIABETES MILLETUS WITH HYPERTENSION WITH CARDIOGENIC SHOCK	C	22-Nov-21
67	IND(CO-AEFI)APVSM21001	2021	39	FEMALE	DEATH	05-03-2021	COVISHIELD	GULLIAN BARRE SYNDROME WITH PNEUMONIA	B1	22-Nov-21
68	IND(CO-AEFI)KEPLK21003	2021	40	FEMALE	HOSPITALIZED & RECOVERED	04-03-2021	COVISHIELD	ACUTE DISSEMINATED ENCEPHALOMYELITIS	B1	22-Nov-21
69	IND(CO-AEFI)CGMGL21001	2021	51	FEMALE	HOSPITALIZED & RECOVERED	08-03-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
70	IND(CO-AEFI)WBNDG21001	2021	71	FEMALE	DEATH	19-03-2021	COVISHIELD	ACUTE ANTERIOR WALL MYOCARDIAL INFARCTION WITH TYPE II DIABETES MELLITUS	C	22-Nov-21
71	IND(CO-AEFI)GOGON21003	2021	35	MALE	HOSPITALIZED & RECOVERED	15-02-2021	COVISHIELD	MILD COVID DISEASE	C	22-Nov-21

CAUSALITY CLASSIFICATION OF 178 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 22 NOV 2021- (NEW DELHI)

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72	IND(CO-AEFI)KEPTM21003	2021	81	FEMALE	HOSPITALIZED & RECOVERED	20-03-2021	COVISHIELD	ACUTE INFERIOR WALL MYOCARDIAL INFARCTION WITH UNDERLYING DIABETES, HYPERTENSION & DYSLIPIDEMIA.	C	22-Nov-21
73	IND(CO-AEFI)HAHSR21004	2021	68	FEMALE	DEATH	22-03-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
74	IND(CO-AEFI)HAKTL21001	2021	61	FEMALE	HOSPITALIZED & RECOVERED	18-03-2021	COVISHIELD	ACCELERATED HYPERTENSION	C	22-Nov-21
75	IND(CO-AEFI)WBSPG21002	2021	66	MALE	DEATH	19-03-2021	COVISHIELD	ACUTE CORONARY SYNDROME WITH UNDRLYING DIABETES, HYPERTENSION AND CHRONIC SMOKING	C	22-Nov-21
76	IND(CO-AEFI)UPBDH21001	2021	73	MALE	DEATH	17-03-2021	COVISHIELD	COVID 19 DISEASE WITH ACUTE RESPIRATORY DISTRESS SYNDROME WITH UNDERLYING DIABETES MELLITUS AND HYPERTENSION	C	22-Nov-21
77	IND(CO-AEFI)UPBBK21001	2021	55	MALE	HOSPITALIZED & RECOVERED	17-03-2021	COVISHIELD	FEVER AND BODY ACHE	A1	22-Nov-21
78	IND(CO-AEFI)MPBPL21001	2021	35	FEMALE	SEVERE & RECOVERED	16-01-2021	COVISHIELD	ACUTE FEBRILE ILLNESS	A1	22-Nov-21
79	IND(CO-AEFI)MPBTL21001	2021	32	MALE	HOSPITALIZED & RECOVERED	11-02-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
80	IND(CO-AEFI)KABEL21008	2021	76	MALE	DEATH	26-03-2021	COVISHIELD	ACUTE MYOCARDIAL INFARCTION IN A KNOWN CASE OF DIABETES MELLITUS AND HYPERTENSION.	C	22-Nov-21
81	IND(CO-AEFI)DLNDL21004	2021	61	MALE	DEATH	25-03-2021	COVISHIELD	ACUTE CORONARY SYNDROME LEADING TO MYOCARDIAL INFARCTION AND PULMONARY EDEMA	C	22-Nov-21
82	IND(CO-AEFI)GOGOS21005	2021	63	MALE	HOSPITALIZED & RECOVERED	24-03-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
83	IND(CO-AEFI)GOGOS21006	2021	62	MALE	HOSPITALIZED & RECOVERED	09-03-2021	COVISHIELD	COVID 19 DISEASE	C	22-Nov-21
84	IND(CO-AEFI)KEAPZ21017	2021	63	MALE	HOSPITALIZED & RECOVERED	27-03-2021	COVISHIELD	CORONARY ARTERY DISEASE WITH ACUTE CORONARY SYNDROME (NSTEMI)	C	22-Nov-21
85	IND(CO-AEFI)RJSKR21001	2021	66	MALE	DEATH	26-03-2021	COVISHIELD	ACUTE MYOCARDIAL INFARCTION with underlying COPD and chronic smoking	C	22-Nov-21
86	IND(CO-AEFI)MPBRW21003	2021	59	FEMALE	DEATH	03-02-2021	COVISHIELD	SEVERE COVID 19 DISEASE	C	22-Nov-21
87	IND(CO-AEFI)UPHTR21001	2021	50	FEMALE	HOSPITALIZED & RECOVERED	28-01-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
88	IND(CO-AEFI)WBCAL21026	2021	74	MALE	HOSPITALIZED & RECOVERED	30-03-2021	COVISHIELD	FEVER, JOINT PAIN, VOMITTING AND SYNCOPE	A1	22-Nov-21
89	IND(CO-AEFI)WBMBD21012	2021	63	MALE	DEATH	31-03-2021	COVISHIELD	ACUTE MYOCARDIAL INFARCTION WITH PREVIOUS HISTORY OF CORONARY ARTERY DISEASE AND CHRONIC SMOKER	C	22-Nov-21
90	IND(CO-AEFI)KEAPZ21007	2021	68	MALE	DEATH	12-03-2021	COVISHIELD	SEVERE COVID 19 PNEUMONIA WITH RESPIRATORY FAILURE WITH UNDERLYING DIABETES, HYPERTENSION AND CORONARY ARTERY DISEASE WITH RENAL FAILURE	C	22-Nov-21
91	IND(CO-AEFI)MPBRW21004	2021	67	MALE	DEATH	01-04-2021	COVISHIELD	SEVERE COVID DISEASE	C	22-Nov-21
92	IND(CO-AEFI)ORNRP21002	2021	66	MALE	DEATH	01-04-2021	COVISHIELD	SUDDEN CARDIAC DEATH WITH POST MORTEM CONFIRMED ATHEROVASCULAR DISEASE	C	22-Nov-21
93	IND(CO-AEFI)KEAPZ21008	2021	56	MALE	DEATH	06-03-2021	COVISHIELD	ACUTE MYOCARDIAL INFARCTION with underlying Diabetes	C	22-Nov-21
94	IND(CO-AEFI)TNCNI21006	2021	33	MALE	HOSPITALIZED & RECOVERED	03-03-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
95	IND(CO-AEFI)KABMP21017	2021	66	MALE	HOSPITALIZED & RECOVERED	06-03-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
96	IND(CO-AEFI)WBMBD21015	2021	45	FEMALE	HOSPITALIZED & RECOVERED	23-03-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
97	IND(CO-AEFI)MPMDL21003	2021	73	FEMALE	HOSPITALIZED & RECOVERED	22-03-2021	COVISHIELD	COVID 19 DISEASE WITH UNDERLYING HYPERTENSION	C	22-Nov-21
98	IND(CO-AEFI)MHBMC21041	2021	68	FEMALE	SEVERE & RECOVERED	26-03-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
99	IND(CO-AEFI)WBDMD21008	2021	34	MALE	SEVERE & RECOVERED	05-03-2021	COVISHIELD	MILD COVID 19 INFECTION	C	22-Nov-21
100	IND(CO-AEFI)CGRGH21002	2021	65	FEMALE	HOSPITALIZED & RECOVERED	17-03-2021	COVISHIELD	HYPERTENSION	C	22-Nov-21
101	IND(CO-AEFI)TNCNI21009	2021	59	FEMALE	HOSPITALIZED & RECOVERED	19-01-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21

CAUSALITY CLASSIFICATION OF 178 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 22 NOV 2021- (NEW DELHI)

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A3 - IMMUNIZATION ERROR RELATED REACTION

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C - COINCIDENTAL - UNDERLYING OR EMERGING CONDITION(S), OR CONDITIONS CAUSED BY EXPOSURE TO SOMETHING OTHER THAN VACCINE

D - UNCLASSIFIABLE

S. NO.	NATIONAL ID	YEAR	AGE (IN YEARS)	SEX	REASON FOR REPORTING/ OUTCOME	DATE OF VACCINATION (DD/MM/YYYY)	VACCINE	DIAGNOSIS	CLASSIFICATION* BY NATIONAL AEFI COMMITTEE	DATE OF APPROVAL BY NATIONAL AEFI COMMITTEE
102	IND(CO-AEFI)WBBDN21011	2021	58	FEMALE	HOSPITALIZED & RECOVERED	03-04-2021	COVISHIELD	FEVER, NAUSEA, VOMITING	A1	22-Nov-21
103	IND(CO-AEFI)GOGON21008	2021	56	MALE	HOSPITALIZED & RECOVERED	24-03-2021	COVISHIELD	COVID 19 PNEUMONIA WITH HYPERTENSION AND TYPE 2 DIABETES MELLITUS	C	22-Nov-21
104	IND(CO-AEFI)RJUDP21003	2021	61	MALE	HOSPITALIZED & RECOVERED	03-04-2021	COVISHIELD	NSTEMI WITH BILATERAL ATYPICAL PNEUMONITIS WITH HYPERTENSION, DIABETES MELLITUS AND LEFT VENTRICULAR HYPERTROPHY	C	22-Nov-21
105	IND(CO-AEFI)UPMRD21006	2021	49	MALE	HOSPITALIZED & RECOVERED	05-04-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
106	IND(CO-AEFI)GOGOS21008	2021	87	FEMALE	HOSPITALIZED & RECOVERED	04-03-2021	COVISHIELD	TYPE 2 DIABETES MELLITUS WITH ALZHEIMER WITH HYPERTENSIVE EMERGENCY WITH LEFT VENTRICULAR FAILURE	C	22-Nov-21
107	IND(CO-AEFI)UPBJN21004	2021	67	MALE	DEATH	01-04-2021	COVAXIN	UNEXPLAINED DEATH	D	22-Nov-21
108	IND(CO-AEFI)KEKNU21007	2021	24	FEMALE	HOSPITALIZED & RECOVERED	25-02-2021	COVISHIELD	MILD COVID 19 DISEASE	C	22-Nov-21
109	IND(CO-AEFI)GOGON21009	2021	55	MALE	HOSPITALIZED & RECOVERED	18-03-2021	COVISHIELD	MODERATE COVID 19 DISEASE WITH HYPERTENSION	C	22-Nov-21
110	IND(CO-AEFI)GOGON21010	2021	46	MALE	HOSPITALIZED & RECOVERED	20-03-2021	COVISHIELD	MILD COVID 19 DISEASE IN A KNOWN CASE OF DIABETES MELLITUS	C	22-Nov-21
111	IND(CO-AEFI)KAMYS21007	2021	51	MALE	HOSPITALIZED & RECOVERED	26-03-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
112	IND(CO-AEFI)WBUDJ21006	2021	55	MALE	DEATH	06-03-2021	COVISHIELD	COVID 19 DISEASE, PNEUMONIA AND ARDS	C	22-Nov-21
113	IND(CO-AEFI)HPMND21005	2021	61	MALE	DEATH	12-04-2021	COVISHIELD	ACUTE MYOCARDIAL INFARCTION WITH POST MORTEM CONFIRMED ATHEROVASCULAR DISEASE	C	22-Nov-21
114	IND(CO-AEFI)WBBDN21013	2021	60	FEMALE	DEATH	26-03-2021	COVISHIELD	COVID 19 DISEASE WITH HYPERTENSION AND HYPOTHYROIDISM	C	22-Nov-21
115	IND(CO-AEFI)WBBDN21012	2021	50	FEMALE	HOSPITALIZED & RECOVERED	03-04-2021	COVISHIELD	FEVER AND GASTRITIS	A1	22-Nov-21
116	IND(CO-AEFI)UPMAI21001	2021	37	FEMALE	SEVERE & RECOVERED	05-02-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
117	IND(CO-AEFI)KEIDK21003	2021	60	FEMALE	HOSPITALIZED & RECOVERED	05-04-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
118	IND(CO-AEFI)MPCDW21001	2021	63	MALE	DEATH	17-03-2021	COVISHIELD	BILATERAL PNEUMONIA WITH RESPIRATORY FAILURE	C	22-Nov-21
119	IND(CO-AEFI)GOGON21014	2021	79	MALE	HOSPITALIZED & RECOVERED	31-03-2021	COVISHIELD	COVID 19 DISEASE WITH UNDERLYING DIABETES MELLITUS, HYPERTENSION, ISCHEMIC HEART DISEASE, CHRONIC KIDNEY DISEASE	C	22-Nov-21
120	IND(CO-AEFI)KABEL21010	2021	62	FEMALE	DEATH	01-04-2021	COVISHIELD	COVID 19 PNEUMONIA WITH SEPSIS WITH RENAL FAILURE	C	22-Nov-21
121	IND(CO-AEFI)PBPTL21007	2021	64	MALE	SEVERE & RECOVERED	11-04-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
122	IND(CO-AEFI)MPSNI21005	2021	68	FEMALE	DEATH	22-03-2021	COVISHIELD	SEVERE COVID 19 PNEUMONIA	C	22-Nov-21
123	IND(CO-AEFI)GOGOS21011	2021	62	MALE	HOSPITALIZED & RECOVERED	26-03-2021	COVISHIELD	MILD COVID-19 PNEUMONIA	C	22-Nov-21
124	IND(CO-AEFI)PDYNM21001	2021	82	MALE	DEATH	08-03-2021	COVISHIELD	SEVERE ACUTE RESPIRATORY ILLNESS	C	22-Nov-21
125	IND(CO-AEFI)GOGOS21010	2021	58	FEMALE	HOSPITALIZED & RECOVERED	26-03-2021	COVISHIELD	MILD COVID 19 DISEASE	C	22-Nov-21
126	IND(CO-AEFI)GOGON21015	2021	55	MALE	HOSPITALIZED & RECOVERED	11-04-2021	COVISHIELD	ACUTE INFERIOR AND POSTERIOR WALL MYOCARDIAL INFARCTION	B1	22-Nov-21
127	IND(CO-AEFI)KEKZK21004	2021	44	FEMALE	HOSPITALIZED & RECOVERED	18-02-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
128	IND(CO-AEFI)WBASN21005	2021	37	MALE	HOSPITALIZED & RECOVERED	22-02-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
129	IND(CO-AEFI)KEAPZ21020	2021	54	FEMALE	HOSPITALIZED & RECOVERED	08-03-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
130	IND(CO-AEFI)PBPTL21002	2021	53	FEMALE	SEVERE & RECOVERED	24-02-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
131	IND(CO-AEFI)PBPTL21003	2021	43	MALE	SEVERE & RECOVERED	26-02-2021	COVISHIELD	FACIAL PALSY	B2	22-Nov-21
132	IND(CO-AEFI)JKKUA21001	2021	21	MALE	DEATH	21-04-2021	COVISHIELD	ANAPHYLACTIC SHOCK	A1	22-Nov-21
133	IND(CO-AEFI)WBCAL21028	2021	28	FEMALE	SEVERE & RECOVERED	19-04-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
134	IND(CO-AEFI)CGRNG21005	2021	46	FEMALE	HOSPITALIZED & RECOVERED	03-04-2021	COVISHIELD	ACUTE FEBRILE ILLNESS	A1	22-Nov-21
135	IND(CO-AEFI)UPBAD21002	2021	55	MALE	DEATH	05-04-2021	COVISHIELD	HEPATITIS C WITH CHRONIC KIDNEY DISEASE	C	22-Nov-21
136	IND(CO-AEFI)WBDJL21013	2021	64	FEMALE	HOSPITALIZED & RECOVERED	06-04-2021	COVISHIELD	CHOLECYSTITIS WITH HYPERTENSION	C	22-Nov-21

CAUSALITY CLASSIFICATION OF 178 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 22 NOV 2021- (NEW DELHI)

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137	IND(CO-AEFI)TRTRW21012	2021	57	FEMALE	HOSPITALIZED & RECOVERED	30-03-2021	COVISHIELD	SEIZURE DISORDER	C	22-Nov-21
138	IND(CO-AEFI)RJJPR21004	2021	48	MALE	HOSPITALIZED & RECOVERED	01-04-2021	COVISHIELD	ACUTE FEBRILE ILLNESS	A1	22-Nov-21
139	IND(CO-AEFI)KETHR21019	2021	70	FEMALE	HOSPITALIZED & RECOVERED	15-04-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
140	IND(CO-AEFI)GOGON21027	2021	78	FEMALE	DEATH	13-03-2021	COVISHIELD	COVID-19 DISEASE	C	22-Nov-21
141	IND(CO-AEFI)WBMNP21005	2021	24	FEMALE	HOSPITALIZED & RECOVERED	27-01-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
142	IND(CO-AEFI)WBAPD21005	2021	42	MALE	SEVERE & RECOVERED	22-02-2021	COVISHIELD	ALLERGIC RASH	A1	22-Nov-21
143	IND(CO-AEFI)KEPLK21013	2021	42	FEMALE	HOSPITALIZED & RECOVERED	21-05-2021	COVISHIELD	SEIZURE DISORDER IN POST-OPERATIVE MENINGIOMA WITH REOCCURRENCE	C	22-Nov-21
144	IND(CO-AEFI)DLSDR21002	2021	28	MALE	HOSPITALIZED & RECOVERED	05-05-2021	COVISHIELD	ACUTE IDIOPATHIC THROMBOCYTOPENIC PURPURA	B1	22-Nov-21
145	IND(CO-AEFI)TNCNI21016	2021	50	FEMALE	DEATH	07-04-2021	COVISHIELD	COVID-19 DISEASE (PNEUMONIA, ACUTE RESPIRATORY DISTRESS SYNDROME, SEPSIS, ACUTE KIDNEY INJURY AND TYPE 1 RESPIRATORY FAILURE)	C	22-Nov-21
146	IND(CO-AEFI)GOGON21033	2021	65	FEMALE	HOSPITALIZED & RECOVERED	28-05-2021	COVISHIELD	ANTERIOR WALL MYOCARDIAL INFARCTION WITH HYPERTENSION	C	22-Nov-21
147	IND(CO-AEFI)TSRGY21005	2021	49	MALE	HOSPITALIZED & RECOVERED	12-04-2021	COVISHIELD	IDIOPATHIC THROMBOCYTOPENIC PURPURA	B1	22-Nov-21
148	IND(CO-AEFI)TSHYD21022	2021	18	FEMALE	DEATH	29-05-2021	COVISHIELD	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	A1	22-Nov-21
149	IND(CO-AEFI)ORRYG21005	2021	19	FEMALE	HOSPITALIZED & RECOVERED	08-06-2021	COVISHIELD	ALLERGIC REACTION, VOMITTING AND PAIN IN ABDOMEN	A1	22-Nov-21
150	IND(CO-AEFI)HAPNP21008	2021	20	MALE	HOSPITALIZED & RECOVERED	21-06-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
151	IND(CO-AEFI)GUSBK21001	2021	25	MALE	HOSPITALIZED & RECOVERED	24-06-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
152	IND(CO-AEFI)MEEKH21004	2021	19	FEMALE	HOSPITALIZED & RECOVERED	14-06-2021	COVISHIELD	FOCAL SEIZURE	B1	22-Nov-21
153	IND(CO-AEFI)KEPLK21017	2021	53	FEMALE	HOSPITALIZED & RECOVERED	29-06-2021	COVISHIELD	ANXIETY REACTION	A4	22-Nov-21
154	IND(CO-AEFI)RJJPR21015	2021	43	FEMALE	HOSPITALIZED & RECOVERED	02-07-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
155	IND(CO-AEFI)MHBMC21099	2021	51	FEMALE	DEATH	03-04-2021	COVISHIELD	SEVERE COVID PNEUMONIA	C	22-Nov-21
156	IND(CO-AEFI)UPPSN21002	2021	58	FEMALE	HOSPITALIZED & RECOVERED	08-07-2021	COVISHIELD	SEIZURE IN A KNOWN CASE OF CVA AND HYPERTENSION	C	22-Nov-21
157	IND(CO-AEFI)WBCAL21032	2021	37	FEMALE	HOSPITALIZED & RECOVERED	26-06-2021	COVISHIELD	ACUTE FEBRILE ILLNESS WITH VOMITING	A1	22-Nov-21
158	IND(CO-AEFI)UPRBL21002	2021	77	MALE	DEATH	17-03-2021	COVISHIELD	COVID 19 PNEUMONIA	C	22-Nov-21
159	IND(CO-AEFI)UPGZA21001	2021	85	MALE	DEATH	09-04-2021	COVISHIELD	SEVERE COVID 19 PNEUMONIA	C	22-Nov-21
160	IND(CO-AEFI)GUJMD21003	2021	22	MALE	HOSPITALIZED & RECOVERED	14-04-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
161	IND(CO-AEFI)KETHR21032	2021	58	FEMALE	HOSPITALIZED & RECOVERED	06-07-2021	COVAXIN	LEFT FOCAL SEIZURES (RIGHT FRONTAL MENINGIOMA) IN A KNOWN CASE OF CARCINOMA THYROID AND HYPOTHYROIDISM	C	22-Nov-21
162	IND(CO-AEFI)KETRM21027	2021	21	FEMALE	HOSPITALIZED & RECOVERED	03-07-2021	COVISHIELD	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	A1	22-Nov-21
163	IND(CO-AEFI)MHTHN21019	2021	36	FEMALE	HOSPITALIZED & RECOVERED	19-03-2021	COVISHIELD	ACUTE DISSEMINATED ENCEPHALOMYELITIS	B1	22-Nov-21
164	IND(CO-AEFI)MHBMC21059	2021	22	MALE	HOSPITALIZED & RECOVERED	29-06-2021	COVISHIELD	SEIZURE	B1	22-Nov-21
165	IND(CO-AEFI)WBNPG21008	2021	62	FEMALE	HOSPITALIZED & RECOVERED	22-05-2021	COVISHIELD	EXFOLIATIVE DERMATITIS WITH SEPSIS WITH URINARY TRACT INFECTION WITH DIABETES MELLITUS WITH HYPERTENSION WITH HYPOTHYROIDISM	B2	22-Nov-21
166	IND(CO-AEFI)WBCAL21033	2021	25	FEMALE	HOSPITALIZED & RECOVERED	22-07-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
167	IND(CO-AEFI)HAJJR21003	2021	31	FEMALE	HOSPITALIZED & RECOVERED	25-01-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
168	IND(CO-AEFI)KETHR21035	2021	23	FEMALE	HOSPITALIZED & RECOVERED	15-07-2021	COVISHIELD	SEIZURE DISORDER? ECLAMPSIA	C	22-Nov-21
169	IND(CO-AEFI)UPGBN21004	2021	47	MALE	DEATH	15-04-2021	COVISHIELD	COVID 19 DISEASE	C	22-Nov-21

CAUSALITY CLASSIFICATION OF 178 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 22 NOV 2021- (NEW DELHI)

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170	IND(CO-AEFI)KETRM21031	2021	56	MALE	HOSPITALIZED & RECOVERED	01-08-2021	COVISHIELD	NON-ST-ELEVATION MYOCARDIAL INFARCTION with AGE-56 YEARS and RISK FACTORS OF SMOKING, ALCOHOL CONSUMPTION WITH FAMILY HISTORY.	C	22-Nov-21
171	IND(CO-AEFI)KEWYD21019	2021	37	MALE	HOSPITALIZED & RECOVERED	19-07-2021	COVISHIELD	ACUTE ANTERIOR WALL MYOCARDIAL INFARCTION	B1	22-Nov-21
172	IND(CO-AEFI)MHBMC21066	2021	19	FEMALE	HOSPITALIZED & RECOVERED	30-07-2021	COVISHIELD	ACUTE FEBRILE ILLNESS	A1	22-Nov-21
173	IND(CO-AEFI)WBDJL21034	2021	32	MALE	SEVERE & RECOVERED	09-08-2021	COVISHIELD	ANAPHYLAXIS	A1	22-Nov-21
174	IND(CO-AEFI)PDPNY21006	2021	20	MALE	HOSPITALIZED & RECOVERED	17-06-2021	COVISHIELD	GUILLAIN BARRE SYNDROME	B1	22-Nov-21
175	IND(CO-AEFI)KEPTM21011	2021	51	FEMALE	HOSPITALIZED & RECOVERED	14-08-2021	COVISHIELD	ALLERGIC BRONCHITIS	C	22-Nov-21
176	IND(CO-AEFI)DLNWE21006	2021	24	FEMALE	HOSPITALIZED & RECOVERED	06-08-2021	COVISHIELD	ALLERGIC REACTION	A1	22-Nov-21
177	IND(CO-AEFI)MPSDL21001	2021	51	MALE	SEVERE & RECOVERED	01-04-2021	COVISHIELD	FOCAL SEIZURE	B1	22-Nov-21
178	IND(CO-AEFI)KEAPZ21040	2021	28	FEMALE	DEATH	07-06-2021	COVISHIELD	THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME	A1	22-Nov-21

*Covid vaccine is a new vaccine. The causality may change as more information become available.

Verified by Dr Anil Gurtoo and Dr Anju Seth on 01 Dec 2021

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Annexure-A16

डॉ. मनोहर अगनानी, भा.प्र.से.
अपर सचिव

DR. MANOHAR AGNANI, IAS
Additional Secretary

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: T-13020/03/2021-Imm
Date: 17 May, 2021

Dear All,

As you may be aware that there is a mechanism to report, investigate, analyse and assess the Adverse Events Following Immunization (AEFI) in the country.

In the light of concerns raised regarding post vaccination embolic and thrombotic events particularly with AstraZeneca-Oxford vaccine [Covishield in India], an in-depth analysis to identify the thromboembolic events (such as Cerebral Venous Sinus Thrombosis, Deep Vein Thrombosis and Pulmonary Embolism) in association with thrombocytopenia (Thrombosis with Thrombocytopenia Syndrome-TTS) following use of COVISHIELD & COVAXIN was conducted.

As per the in-depth analysis of AEFI cases by National AEFI Committee for TTS following COVID-19 vaccination (till 03 April 2021), there is a very miniscule but definitive risk of thromboembolic events following the administration of COVISHIELD vaccine. 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. There were no potential thromboembolic events reported following COVAXIN.

Although, the observed rates have been less than expected rates for such events, MoHFW would continue to monitor the safety of all COVID-19 vaccines and promote reporting of suspected adverse events for investigations and causality assessments. In this regard, National AEFI Committee has prepared 2 advisories viz. 1) ***Advisory for healthcare service providers for Diagnosing and treating Thrombosis and Thrombocytopenic Syndrome (TTS) occurring after administration of COVID-19 vaccine*** & 2) ***Advisory for vaccine beneficiaries to encourage people to encourage reporting of such events to the health system, be***

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aware of TTS and seek medical help (enclosed as Annexure).

You are kindly requested to share the first advisory on TTS with all concerned public & private health institutions and professional bodies like IMA, etc. to provide guidance for Diagnosing and treating Thrombosis and Thrombocytopenic Syndrome (TTS) occurring after administration of COVID-19 vaccine. The second advisory to be circulated to all healthcare workers and made available at such platforms so as to create awareness amongst vaccine beneficiaries.

with kind regards,

Yours sincerely,

Enclosures: As above

17/05/2021

(Dr. Manohar Agnani)

Additional Chief Secretary/Secretary/Principal Secretary, Health & family Welfare, All States/UTs

Copy to:

1. Mission Director (NHM), All States/UTs
2. Additional Secretary & Mission Director (NHM)

Advisory for healthcare service providers

Diagnosing and treating Thrombosis and Thrombocytopenic Syndrome (TTS) occurring after administration of COVID-19 vaccine

Reports of rare cases of thrombosis associated with thrombocytopenia have been reported globally from some countries following the use of some COVID 19 vaccinations particularly AstraZeneca vaccine [Covishield in India] and Johnson & Johnson's Janssen vaccine. These cases have been reported to have occurred within two to three weeks of vaccination, mostly after the first dose; younger than 60 years and women were observed to have a higher risk of the problem. Drug regulators of EU, UK and USA are investigating these reports. A causal relationship between these rare events has not been established at this time[1]. WHO has stated[2] that a causal relationship between the ChAdOx-1S vaccine (AstraZeneca/Covishield) and Thrombosis with Thrombocytopenia Syndrome (TTS) (a very rare syndrome of blood clotting combined with low platelet count reported about 4 to 20 days following vaccination) is considered plausible although the biological mechanism for the syndrome is still being investigated.

In India, the National AEFI Committee has reviewed 498 serious and severe adverse events following COVID-19 vaccinations to identify TTS - thromboembolic events (such as Cerebral Venous Sinus Thrombosis, Deep Vein Thrombosis and Pulmonary Embolism) in association with thrombocytopenia. Only a few cases clinically compatible with the diagnosis of TTS has been identified among these 498 cases which constitute a miniscule part of the total doses administered, such cases were reviewed. If these cases are considered as suspected TTS, the reporting rate of these events in India would be around 0.61/million doses, which is much lower than the 4 cases / million reported by UK's regulator (MHRA) or the 10 cases / million doses reported by Germany. Based on UK's reporting rate, there should have been 360 cases of TTS in India with 9 crore doses administered. Published scientific literature shows that thromboembolic phenomenon is almost 70% less in South East Asian population compared to those of European descent[3,4,5].

Available AEFI data from India does not suggest any overall increase in clotting conditions such as deep venous thrombosis or pulmonary embolism following administration of COVID-19 vaccines. Reported rates of thromboembolic events after COVID-19 vaccines are in line with the expected number of

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[1] EMA Statement: https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots
UK MHRA statement: https://www.gov.uk/government/news/uk-regulator-confirms-that-people-should-continue-to-receive-the-covid-19-vaccine-astrazeneca

[2] WHO-GACVS statement of 21 April: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines_SAGE_recommendation-AZD1222-2021.1

[3] Lee LH, Gallus A, Jindal R, Wang C, Wu CC. Incidence of Venous Thromboembolism in Asian Populations: A Systematic Review. Thromb Haemost. 2017 Dec;117(12):2243-2260. doi: 10.1160/TH17-02-0134. Epub 2017 Dec 6. PMID: 29212112. https://pubmed.ncbi.nlm.nih.gov/29212112/

[4] White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res. 2009;123 Suppl 4:S11-7. doi: 10.1016/S0049-3848(09)70136-7. PMID: 19303496. https://pubmed.ncbi.nlm.nih.gov/19303496/

[5] ZAKAI, N.A. and McCLURE, L.A. (2011), Racial differences in venous thromboembolism. Journal of Thrombosis and Haemostasis, 9: 1877-1882. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1538-7836.2011.04443.x

diagnoses of these conditions. Both conditions occur naturally and are not uncommon. They also occur in patients with COVID-19 infection.

Information for healthcare professionals

Healthcare professionals should be alert to the signs and symptoms of TTS (thromboembolism and thrombocytopenia syndrome), so that they can promptly investigate and treat people affected in line with available guidelines.

Diagnosis and Management

Investigations for any suspected cases of thrombosis and thrombocytopenia:

- Blood
  - Platelet count <150x 10^9/L confirming *Thrombocytopenia*
  - Coagulation screen-raised D-Dimer values (>4000 mcg/L, suspect if the D-dimer level is 2000-4000 mcg/L)
  - Preserve serum sample for Antibodies to platelet factor 4 (PF4) which are detected using ELISA HIT assay.
- Radio-imaging studies
  - CT/MRI specifically for cerebro-vascular sinus thrombosis, haemorrhage, stroke
  - ECHO heart for pulmonary embolism
  - Radio-nucleotide studies and CT chest for pulmonary embolism
  - USG-doppler for thrombus in the portal, splenic, mesenteric veins
  - USG-doppler of the limbs for deep vein thrombosis (DVT)

Unlikely a case of TTS

- Thrombocytopenia without thrombosis with D-dimer normal or near normal and normal fibrinogen level
- Thrombosis with normal platelet count and D-dimer <2000 mcg/L and normal fibrinogen

Management of Thrombosis and Thrombocytopenic Syndrome (TTS) at a tertiary care hospital* such as District Hospital or Medical college, etc.

- Administer intravenous immunoglobulin (IV-Ig) urgently, 1 g/kg (divided into two days if needed) as this is the treatment most likely to influence the disease process.
- CORRECT fibrinogen levels if needed, to ensure level does not drop below 1.5 g/L, using fibrinogen concentrate or cryoprecipitate
- When fibrinogen is >1.5 g/L and platelets >30 x10^9/L consider starting anticoagulation. If anticoagulation is needed before then, critical illness dose Argatroban can be considered, initially without dose escalation and maintained at low dose.
- ANTICOAGULATE with non-heparin-based therapies such as DOACs (Direct-acting oral anti-coagulants), Argatroban, Fondaparinux or Danaparoid depending on the clinical picture. Bleeding and thrombotic risk needs to be carefully balanced and lower doses may be appropriate while platelet count is still low.
- Steroids and plasma exchange should be considered and in particular if there is a delay in giving IV-Ig.
- If no overt thrombosis, but thrombocytopenia with raised D Dimer, thrombo-prophylaxis with non-heparin-based anticoagulants should be considered – balancing bleeding and thrombotic risk. DOAC, fondaparinux or danaparoid can be used.

***Ambulance services should be made available for transportation/referral of the patient to the tertiary care hospital.**

AVOID following Interventions:

- Avoid platelet transfusions. Discuss any required interventions. If neurosurgery is required, this should not be delayed, and if the platelet count is <100 x10^9/L a platelet transfusion will be appropriate after, or with, IV-Ig
- AVOID all forms of heparin including heparin-based flushes. (It is unknown whether heparin exacerbates the condition but until further data is clear, this is best avoided).
- Avoid thrombopoietin receptor agonists and Antiplatelet agents.

At discharge

- Continue anticoagulation for at least 3 months. If thrombosis was only arterial, once the D-dimer, platelets and fibrinogen have returned to normal, the patient can be switched to an antiplatelet agent and continued for three months.
- Monitor the platelet count periodically to observe for possible relapse.

Contraindications for the administration of COVISHIELD in the context of TTS:

Past history of major venous and arterial thrombosis occurring with thrombocytopenia.

Reporting of suspected TTS cases:

- Suspected cases of TTS occurring within 20 days of vaccination should be reported to the vaccinator or the District Immunization Officer (DIO) in the Case Reporting Format for further reporting on Co-WIN app.

Covishield, the COVID-19 vaccine continues to have a definite positive benefit-risk profile, with tremendous potential to mitigate the severity of infections and reduce deaths due to COVID-19 across the world and in India. Over 15.3 crore doses of Covishield vaccine have been administered as of 08th May 2021 in India. The Ministry of Health and Family Welfare will continue to monitor the safety of all COVID-19 vaccines and promote reporting of suspected adverse events.

References:

1. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood
2. https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf
3. https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca#pharmacodynamic-properties

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Advisory for vaccine beneficiaries

Thrombosis and Thrombocytopenia Syndrome (TTS) occurring after administration of COVID-19 vaccine

Reports of rare cases of thrombosis (blood clotting) associated with thrombocytopenia (low platelet counts) – Thrombosis and Thrombocytopenia Syndrome (TTS) - have been reported globally from some countries following the use of some COVID 19 vaccinations particularly AstraZeneca vaccine [Covishield in India] and Johnson & Johnson's Janssen vaccine. The World Health Organization (WHO) and drug regulators of EU, UK and USA are investigating these reports (1, 2). A causal relationship between these rare events has not been established at this time though it is considered to be plausible by WHO (3).

In India, a review of reported 498 serious and severe AEFI cases by National AEFI Committee shows only a few cases clinically compatible with the diagnosis of TTS have been identified. Published scientific literature shows that thromboembolic phenomenon is almost 70% less in South East Asian population compared to those of European descent (4, 5, 6).

Information for vaccine beneficiaries

A vaccine beneficiary vaccinated with any of the COVID-19 vaccines, particularly Covishield and having one or more of the symptoms mentioned below (see BOX) should be suspected to have Thrombosis and Thrombocytopenia Syndrome (TTS). (7)

Symptoms occurring within 20 days after receiving any COVID 19 vaccine
(Recipient should report to the health facility where vaccine was administered)

- Shortness of breath
- Chest Pain
- Pain in limbs / pain on pressing the limbs or swelling in the 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 headaches 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 (includes cranial nerve involvements)
- Persistent vomiting without any obvious reason
- Blurred vision/ pain in eyes/Diplopia
- Mental status change / encephalopathy/ depressed level of consciousness
- Any other symptom or health condition which is of concern to the recipient or the family

Contraindications for the administration of COVISHIELD in the context of TTS:

Past history of major venous and arterial thrombosis occurring with thrombocytopenia.

The Ministry of Health and Family Welfare will continue to monitor the safety of all COVID-19 vaccines and promote reporting, investigation and monitoring of suspected adverse events. Covishield, the COVID-19 vaccine continues to have a definite positive benefit-risk profile, with tremendous potential

to mitigate the severity of infections and reduce deaths due to COVID-19 across the world and in India. Over 15.3 crore doses of Covishield vaccine have been administered as of 08th May 2021 in India.

References:

1. EMA Statement: https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots
2. UK MHRA statement: https://www.gov.uk/government/news/uk-regulator-confirms-that-people-should-continue-to-receive-the-covid-19-vaccine-astrazeneca
3. WHO-GACVS statement of 21 April: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1
4. Lee LH, Gallus A, Jindal R, Wang C, Wu CC. Incidence of Venous Thromboembolism in Asian Populations: A Systematic Review. Thromb Haemost. 2017 Dec;117(12):2243-2260. doi: 10.1160/TH17-02-0134. Epub 2017 Dec 6. PMID: 29212112. https://pubmed.ncbi.nlm.nih.gov/29212112/
5. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res. 2009;123 Suppl 4:S11-7. doi: 10.1016/S0049-3848(09)70136-7. PMID: 19303496. https://pubmed.ncbi.nlm.nih.gov/19303496/
6. ZAKAI, N.A. and McCLURE, L.A. (2011), Racial differences in venous thromboembolism. Journal of Thrombosis and Haemostasis, 9: 1877-1882. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1538-7836.2011.04443.x
7. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

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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;

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- 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.

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(Release ID: 1719293)

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Annexure-A18

डॉ. मनोहर अगनानी, भा.प्र.से.
अपर सचिव

DR. MANOHAR AGNANI, IAS
Additional Secretary

Dear All

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: T.22020/01/2018-Imm
Dated: 11th October 2021

This is in reference to my DO letter No: T-13020/03/2021-Imm dated 17th May 2021 in which advisories for healthcare service providers and vaccine beneficiaries for suspecting, diagnosing, treating and reporting suspected cases of Thrombosis and Thrombocytopenic Syndrome (TTS), reported after administration of COVID-19 vaccines were shared with the States for further dissemination.

However, it has been observed that all such suspected cases of TTS are still not being reported from the districts as these advisories have not been disseminated widely among health care professionals in districts. Clinicians might have come across such cases but are not aware of details of the District Immunization Officer/District RCHO to whom these cases need to be reported and what are the standard treatment protocols to manage the same.

Therefore, you are kindly requested to disseminate the following immediately: -

- First advisory on TTS with the concerned public and private health institutions (including medical colleges, district hospitals, private hospitals, etc.) and professional bodies like IMA, IAP, FOGSI, Indian Association of Physicians, etc. to provide guidance for Diagnosing and treating Thrombosis and Thrombocytopenic Syndrome (TTS) occurring after administration of COVID-19 vaccine.
- Second advisory to all healthcare workers so as to create awareness amongst vaccine beneficiaries on seeking treatment as soon as possible for any suspected cases of TTS.

The DIOs/DRCHOs may be instructed to share their contact details (email and mobile numbers) with medical professionals in districts so that all serious and severe AEFIs (including suspected TTS cases) can be reported to the system for further necessary actions related to investigations, causality assessments and risk assessments.

Yours sincerely.

Enclosures: As above

(Dr. Manohar Agnani)

Additional Chief Secretary/Secretary/Principal Secretary, Health & family Welfare, All States/UTs

Copy to:

1. Mission Director (NHM), All States/UTs
2. Additional Secretary & Mission Director (NHM)
3. Chairperson, State AEFI Committees
4. SEPIO, All States/UTs
5. Representative, WHO-ICO
6. Chairperson, National AEFI Committee

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Annexure A19

Z-16025/05/2012 Imm p/f
Government of India
Ministry of Health & Family Welfare
Immunization Division

Nirman Bhawan, New Delhi
Date: 05th November 2021

Causality assessment results of 22 reported Serious Adverse Events Following Immunization (AEFI) cases following COVID-19 vaccination approved by National AEFI Committee on 18th October 2021.

The Immunization Division, MOHFW has taken several steps to strengthen the national AEFI surveillance system for COVID-19 vaccinations. Considering the importance and critical nature of the task, steps were taken to include medical specialists, cardiologists, neurologists, pulmonary medicine specialists, obstetrician-gynecologist as members of the causality assessment sub-committee at the national level. A Special Group has been framed to conduct causality assessment of AEFIs following COVID-19 vaccination. The results of causality assessment done by this Special Group is discussed in the national AEFI committee meeting for final approval.

The results of the causality assessment for 22 cases completed on 18th October 2021 after thorough review, deliberation and approval by the National AEFI Committee is given in the annexure (anonymized line list of the causality assessment done by the National AEFI Committee).

09 out of 22 cases for which Causality assessment has been done were found to have **consistent causal association to vaccination.** Of these 09 cases, 05 cases were vaccine product related reaction and 04 cases were immunization anxiety related reaction. 12 cases have inconsistent causal association to vaccination (**coincidental - not linked to vaccination**), including 05 death cases. There was 01 case (death) in indeterminate category.

Vaccine product related reactions are expected reactions that can be attributed to vaccination based on current scientific evidence. Examples of such reactions are allergic reactions and anaphylaxis, etc.

Indeterminate reactions are reactions which have occurred soon after vaccination but there is no definitive evidence in current literature or clinical trial data that this event could have been caused due to the vaccine. Further observations, analysis and studies are required.

Unclassifiable events are events which have been investigated but there is not enough evidence for assigning a diagnosis due to missing crucial information. When this relevant information becomes available, the case may be reconsidered for causality assessment.

Coincidental events are events that are reported following immunization but for which a clear cause other than vaccination is found on investigation.

Overall, the benefits of vaccination are overwhelmingly greater than the small risk of harm. However, as a measure of utmost precaution, all emerging signals of harm are being constantly tracked and reviewed periodically.

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CAUSALITY CLASSIFICATION OF 22 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 18 OCT 2021- (NEW DELHI)

A1 - VACCINE PRODUCT RELATED REACTION

A2 - VACCINE QUALITY DEFECT RELATED REACTION

A3 - IMMUNIZATION ERROR RELATED REACTION

A4 - IMMUNIZATION ANXIETY RELATED REACTION

B1 - TEMPORAL RELATIONSHIP IS CONSISTENT BUT THERE IS INSUFFICIENT DEFINITIVE EVIDENCE FOR VACCINE CAUSING EVENT

B2 - REVIEWING FACTORS RESULT IN CONFLICTING TRENDS OF CONSISTENCY AND INCONSISTENCY WITH CAUSAL ASSOCIATION TO IMMUNIZATION

C - COINCIDENTAL - UNDERLYING OR EMERGING CONDITION(s), OR CONDITIONS CAUSED BY EXPOSURE TO SOMETHING OTHER THAN VACCINE

D - UNCLASSIFIABLE

S. NO.	NATIONAL ID	YEAR	AGE (IN YEARS)	SEX	REASON FOR REPORTING/ OUTCOME	DATE OF VACCINATION (DD/MM/YYYY)	VACCINE	DIAGNOSIS	CLASSIFICATION* BY NATIONAL AEFI COMMITTEE	DATE OF APPROVAL BY NATIONAL AEFI COMMITTEE
1	IND(CO-AEFI)KABMP21002	2021	42	FEMALE	HOSPITALIZED AND RECOVERED	18-01-2021	COVISHIELD	ANXIETY REACTION	A4	18-10-2021
2	IND(CO-AEFI)KACDG21001	2021	50	FEMALE	HOSPITALIZED AND RECOVERED	18-01-2021	COVISHIELD	ANXIETY REACTION	A4	18-10-2021
3	IND(CO-AEFI)KEKZK21001	2021	44	FEMALE	HOSPITALIZED AND RECOVERED	21-01-2021	COVISHIELD	FEVER, HEADACHE AND VOMITING	A1	18-10-2021
4	IND(CO-AEFI)MPMDS21001	2021	26	MALE	HOSPITALIZED AND RECOVERED	16-01-2021	COVISHIELD	ANXIETY REACTION	A4	18-10-2021
5	IND(CO-AEFI)ORBGH21003	2021	28	FEMALE	HOSPITALIZED AND RECOVERED	16-01-2021	COVISHIELD	PNEUMONIA (COVID POSITIVE)	C	18-10-2021
6	IND(CO-AEFI)TSRJS21002	2021	36	FEMALE	HOSPITALIZED AND RECOVERED	18-01-2021	COVISHIELD	NON CARDIAC CHEST PAIN	C	18-10-2021
7	IND(CO-AEFI)MPBHP21001	2021	45	MALE	DEATH	17-02-2021	COVISHIELD	COVID 19 DISEASE	C	18-10-2021
8	IND(CO-AEFI)ORGJM21001	2021	30	FEMALE	HOSPITALIZED AND RECOVERED	19-02-2021	COVISHIELD	CVA (MULTIPLE INFARCTS) IN KNOWN CASE OF TAKAYASU ARTERITIS	C	18-10-2021
9	IND(CO-AEFI)ORSUN21004	2021	25	MALE	HOSPITALIZED AND RECOVERED	18-01-2021	COVISHIELD	ALLERGIC RASH	A1	18-10-2021
10	IND(CO-AEFI)WBDMD21007	2021	45	FEMALE	HOSPITALIZED AND RECOVERED	02-03-2021	COVISHIELD	CVA (ACUTE ISCHEMIC INFARCT- LEFT BASAL GANGLIA) WITH HYPERTENSION	C	18-10-2021
11	IND(CO-AEFI)WBMBD21004	2021	21	FEMALE	SEVERE AND RECOVERED	25-01-2021	COVISHIELD	ANAPHYLAXIS	A1	18-10-2021
12	IND(CO-AEFI)WBSPG21001	2021	76	MALE	DEATH	09-03-2021	COVISHIELD	ACUTE CORONARY SYNDROME WITH UNDERLYING DIABETES MELLITUS, HYPERTENSION AND COPD	C	18-10-2021

CAUSALITY CLASSIFICATION OF 22 AEFI CASES APPROVED BY THE NATIONAL AEFI COMMITTEE ON 18 OCT 2021- (NEW DELHI)

A1 - VACCINE PRODUCT RELATED REACTION

A2 - VACCINE QUALITY DEFECT RELATED REACTION

A3 - IMMUNIZATION ERROR RELATED REACTION

A4 - IMMUNIZATION ANXIETY RELATED REACTION

B1 - TEMPORAL RELATIONSHIP IS CONSISTENT BUT THERE IS INSUFFICIENT DEFINITIVE EVIDENCE FOR VACCINE CAUSING EVENT

B2 - REVIEWING FACTORS RESULT IN CONFLICTING TRENDS OF CONSISTENCY AND INCONSISTENCY WITH CAUSAL ASSOCIATION TO IMMUNIZATION

C - COINCIDENTAL - UNDERLYING OR EMERGING CONDITION(S), OR CONDITIONS CAUSED BY EXPOSURE TO SOMETHING OTHER THAN VACCINE

D - UNCLASSIFIABLE

S. NO.	NATIONAL ID	YEAR	AGE (IN YEARS)	SEX	REASON FOR REPORTING/ OUTCOME	DATE OF VACCINATION (DD/MM/YYYY)	VACCINE	DIAGNOSIS	CLASSIFICATION* BY NATIONAL AEFI COMMITTEE	DATE OF APPROVAL BY NATIONAL AEFI COMMITTEE
13	IND(CO-AEFI)UPMZP21001	2021	46	MALE	DEATH	15-03-2021	COVISHIELD	HEMORRHAGIC CVA WITH HYPERTENSION	C	18-10-2021
14	IND(CO-AEFI)KARMN21001	2021	36	FEMALE	HOSPITALIZED AND RECOVERED	20-01-2021	COVISHIELD	ACUTE GASTRITIS	C	18-10-2021
15	IND(CO-AEFI)WBBDN21005	2021	78	MALE	DEATH	23-03-2021	COVISHIELD	LOBAR PNEUMONIA WITH EMPHYSEMA WITH PULMONARY ALVEOLAR PROTEINACEOUS WITH INTERSTITIAL LUNG DISEASE WITH PROLIFERATIVE GLOMERULONEPHRITIS	C	18-10-2021
16	IND(CO-AEFI)HAKNL21003	2021	45	FEMALE	HOSPITALIZED AND RECOVERED	29-01-2021	COVISHIELD	ANAPHYLAXIS	A1	18-10-2021
17	IND(CO-AEFI)WBDJL21010	2021	73	FEMALE	HOSPITALIZED AND RECOVERED	18-03-2021	COVISHIELD	POST STROKE EPILEPSY	C	18-10-2021
18	IND(CO-AEFI)KAC8P21003	2021	27	FEMALE	HOSPITALIZED AND RECOVERED	19-02-2021	COVISHIELD	EPILEPSY	C	18-10-2021
19	IND(CO-AEFI)GUGNR21003	2021	48	FEMALE	DEATH	25-03-2021	COVISHIELD	SUDDEN CARDIAC DEATH WITH DIABETES MELLITUS AND CORONARY ARTERY DISEASE	C	18-10-2021
20	IND(CO-AEFI)GOGOS21018	2021	20	FEMALE	HOSPITALIZED AND RECOVERED	27-06-2021	COVISHIELD	ANAPHYLAXIS	A1	18-10-2021
21	IND(CO-AEFI)GUGNR21006	2021	21	FEMALE	HOSPITALIZED AND RECOVERED	27-07-2021	COVISHIELD	VASOVAGAL REACTION	A4	18-10-2021
22	IND(CO-AEFI)TNCBE21001	2021	20	FEMALE	DEATH	08-06-2021	COVISHIELD	MULTISYSTEM INFLAMMATORY SYNDROME OF CHILDREN	B1	18-10-2021

*Covid vaccine is a new vaccine. The causality may change as more information become available.

Verified by Dr Anil Gurtoo and Dr Anju Seth on 25th October 2021

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	Brighton Case Definition Status
AESI included because they are seen with COVID-19 Disease [3,4]	
Acute respiratory distress syndrome	Submitted (Vaccine)
Multisystem inflammatory syndrome (children & adults)	Submitted (Vaccine)
Acute cardiovascular injury *(includes: myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)*	Myocarditis/pericarditis near completion. Others not yet started
Coagulation disorder *(includes: thrombotic disorders, bleeding disorders)*	Thrombosis near completion; Bleeding disorder WG to be formed
Anosmia, ageusia	WG to be formed
Chilblain – like lesions	WG to be formed
Erythema multiforme	Not yet started
Single Organ Cutaneous Vasculitis	Published
Acute kidney injury	Published lab-based criteria (see *)
Acute liver injury	Published lab-based criteria (see #)
Acute pancreatitis [NEW (Dec 2020)]	Not yet started
Rhabdomyolysis [NEW (Dec 2020)]	Not yet started
Subacute thyroiditis [NEW (Dec 2020)]	Not yet started
AESI included because they have a proven or theoretical association with immunization in general	
Anaphylaxis [1,2]	Published
Thrombocytopenia[1,2,3,4]	Published
Generalized convulsion[1,2]	Published
Acute disseminated encephalomyelitis[4]	Published
Guillain Barré Syndrome[3,4]	Published
AESI included because they have a proven or theoretical association with specific vaccine platform(s)	
Acute aseptic arthritis [r-VSV]	Published
Aseptic meningitis [Live vaccines]	Published
Encephalitis / Encephalomyelitis [Live vaccines]	Published
Idiopathic Peripheral Facial Nerve Palsy [Intranasal EColi Heat Labile Toxin Adjuvanted Vaccine]	Published
Vaccine associated enhanced disease [1(Formalin inactivated measles/RSV; HIV), 2(Chimeric YF Dengue), 5 (SARS / MERS-CoVs)]	In press (Vaccine)

[1] Proven association with immunization encompassing several different vaccines
[2] Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines
[3] Theoretical concern based on wild type disease immunopathogenesis
[4] Theoretical concern related to viral replication during wild type disease
[5] Theoretical concern because it has been demonstrated in an animal model with ≥ 1 vaccine platform
** Acute kidney injury – international consensus definition proposed by the Kidney Disease Improving Global Outcomes expert consensus group (www.kdigo.org)*

- *Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; OR*
- *Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR*
- *Urine volume ≤0.5 ml/ kg/ hour for 6 hours*

 # Acute liver injury – definition as used in majority of COVID-19 publications (but no international consensus):

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- *> 3-fold elevation above the upper normal limit for ALT or AST OR*
- *> 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP*

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