Clinical Research and Validation Management Framework (CRVMF)

for

Accelerating Discovery Research to Early Development for Biopharmaceuticals - "Innovate in India" (I-3)

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LIST OF ABBREVIATIONS

1. DBT – Department of Biotechnology
2. CDSCO – Central Drugs Standard Control Organization
3. CT – Clinical Trial
4. CPCSEA – Committee for the purpose of control and supervision of experiments oan animals
5. IAEC – Institutional animal ethics committee
6. INSA – Indian National Science Academy
7. DCA – The Drugs and Cosmetics Act
8. DCGI – Drug Controller General of India
9. SEC – Subject Expert Committee
10. TRC – Technical Review Committee
11. CLAA – Central Licenses Approving Authority
12. MDAC – Medical Devices Advisory Committee
13. NDAC – New Drugs Advisory Committee
14. INDs – Investigational New Drugs
15. BIS – Bureau of Indian Statistics
16. ISO – International Organization for Drugs Technical Advisory Board
17. DATB – Drugs Technical Advisory Board
18. SDC – State Drug Controller
19. SDRA – State Drug Regulatory Authority
20. RDAC – Recombinant DNA Advisory Committee
21. IBSC – Institutional Biosafety Committees
22. GEAC – Genetic Engineering Approval Committee
23. SBCC – State Biosafety Coordination Committees
24. DLC – District Level Committees
25. RCGM – Review Committee on Genetic Manipulation
26. MoE&F – Ministry of Environment & Forests
27. CTRI – Clinical Trials Registry – India
28. SAE – Serious Adverse Events
29. IEC – Institutional Ethics Committees
30. DGHS – Directorate General of Health Services
31. GLP – Good Laboratory Practices
32. GCP – Good Clinical Practices
33. GVP – Good Pharmacovigilance Practices
34. GPP– Good Participatory Practices
35. PDU – Project Development Unit
36. PMU – Prjoect Management Unit

1. BACKGROUND

The National Biotechnology Development Strategy 2015-2020 announced by the Department of Biotechnology (DBT) lays emphasis on Making India ready to meet the challenge of achieving US $100 billion biotech industry by 2025. The focus is on generation of biotech products, processes and technologies for affordable and accessible health care, promoting innovation R&D, establishing India as world class biomanufacturing hub, and building the required skilled workforce. To achieve this, it is important to promote industry – academia interface and enable the start-ups and small and medium enterprises to build translational innovation research capacities for affordable healthcare product development.

In the public health arena in India, there is an enormous burden of communicable and non-communicable diseases which reflect the necessity to develop tailored solutions towards addressing health needs specific to the disease burden. Vaccines have emerged as the most effective solution for prevention of communicable disease but there are diseases in India for which efficacious vaccines are yet not available. Additionally, development of biosimilars and novel biologics has also become essential for designing affordable solutions against high burden non-communicable disease. Also to address the disease burden development of medical devices and diagnostic tools are a necessity.

The India biopharmaceutical market accounts for 2% of global market. The Indian vaccine market is 3.5% of the total global vaccine market. Current CAGR is at ~18%, but it is estimated that introduction of newer vaccines would enhance this current growth rate. The Indian biosimilar market is 2% of the total global biosimilar market. Strengthening of this sector could lead to capture 4% of the global bio similar market by 2020 if the growth rate is accelerated at 26% CAGR. Indian medical device market is worth $10.3B. The sector is expected to continue witnessing double-digit growth with an estimation to grow at ~28% CAGR and reach $50B by 2025 if the current ecosystem is sustained.

The Indian biopharmaceutical industry faces stiff competition from China, Korea in respect to innovation. The challenge today is not only ensuring a rapid industrial growth for domestic and global market, but developing innovative, affordable and accessible products for public health needs. Innovation is one of the key driving forces behind the sustainable growth of the biopharmaceutical industry and an important determinant of a nation's potential for economic growth and global competitiveness.

The success of biopharmaceutical innovation programs requires strengthening of biotechnological sub-disciplines such as translational research (including discovery and validation), early development and clinical development capacities and manufacturing capabilities. There is a need for establishing accessible bio-manufacturing or CMC units, which are Good Manufacturing Practices (cGMP) and Good Laboratory Practices (cGLP) compliant, are product-agnostic, have varied capabilities for modern enabling technologies, and are modelled to operate in a non-competitive phase for the sustainable growth of the biopharmaceutical industry.

To achieve the desired goals, the need was felt for an integrated Mission Programme addressing key challenges of the sector involving all stakeholders. For designing the Mission Programme an assessment of key strengths and gaps was essential. A Detailed Mapping was done and three landscape documents were prepared– 'Analytical Report forAccelerating Biopharmaceutical innovation in India' a mapping report of the Intellectual Property - "Situational Analysis of the Early Stage Discovery Landscape in the Indian Bio-pharma Sector" and a report on Human Resource gaps and needs "Talent Mapping: BioPharma R&D". Based on these feasibility reports, challenges, gaps and needs were identified.

1.1 PROGRAM OVERVIEW

1.1.1 MISSION OF THE PROGRAM

Enable and nurture an ecosystem for preparing India's technological and product development capabilities in biopharmaceuticals to a level that will be globally competitive over the next decade, and transform the health standards of India's population.

1.1.2 GOAL OF THE PROGRAM

The Mission Programme would be a PAN-India Programme with the main aim of enabling and nurturing the ecosystem for Innovation Research and Product Development capabilities in Bio-pharmaceuticals to enable the sector to be globally competitive over the next decade and transform the health of Indian population. Through these efforts it is proposed that India would work towards achieving its target of $100 billion Biotech Industry by 2025 and also capturing 5% of the Global Biopharmaceutical market share. This Mission is designed in a manner in which it addresses the key components of the Vision outlined in the National Missions -Make in India and Start up India and also aims to take forward the commitments made by DBT in the National Biotechnology Development Strategy.

The mission will focus on:

- Development of product leads that are at advanced stages of the product development lifecycle and relevant to the public health need by focusing on managed partnerships
- Establishing and strengthening shared infrastructure facilities and product discovery/validation and manufacturing
- Developing human capital by providing specific trainings to address the critical skills gap among nascent biotech companies across the product development value chain, including in business plan development, and market penetration.
- Creating and enhancing technology transfer and intellectual property management capacities and capabilities in public and private sector.

1.1.3 OBJECTIVES

1. Foster PDPs for the acceleration of the discovery-to-product commercialization process

2. Strengthen shared infrastructure facilities for research and manufacturing
3. Build and strengthen domain-specific knowledge, skills, and management
4. Provide technical assistance for actors in the industry ecosystem and program Management.

Specific objectives and activities are:

i. Development of specific affordable products:

Development of affordable and accessible biopharmaceuticals (vaccines and biosimilars) and medical devices & diagnostics relevant to public health needs of India by supporting Public and Private institutions researchers and start ups and entrepreneurs that have established proof of concept and are on the path of product development.

ii. Establishment and strengthening of shared infrastructure:

Creating an enabling environment by strengthening existing infrastructure, building effective collaborative partnerships for development of cutting-edge technologies, enhancing clinical expertise and accelerating translational research that would aid in current product development and future pipeline development and enhanced outsourcing capabilities. Components of this section are:

A. Establishing shared facilities that are accessible, equipped with state-of-the-art infrastructure and relevant talent:
   - GLP Validation and Reference Laboratory for standardized bio-analytical and biological characterization
   - CMC Facilities for Early Development for manufacturing of pilot lots of biopharmaceuticals
   - Med-Tech Validation Facility for prototyping and validation of medical devices and diagnostics during early stages of development and testing.
   - Cell Line repository for storage and maintenance of well characterized cell lines and expression systems

B. Building a consortium of partners, in-country& global network of research entities, for development of innovative technologies and platforms:
   - Network of laboratories for:
     i. Translational & interdisciplinary research for developing and validating novel assays/technologies/biomarkers
     ii. Development of cell lines and expression systems
   - Process Development Laboratory
   - Clinical Trial Network

iii. Building and strengthening domain specific knowledge and management skills:

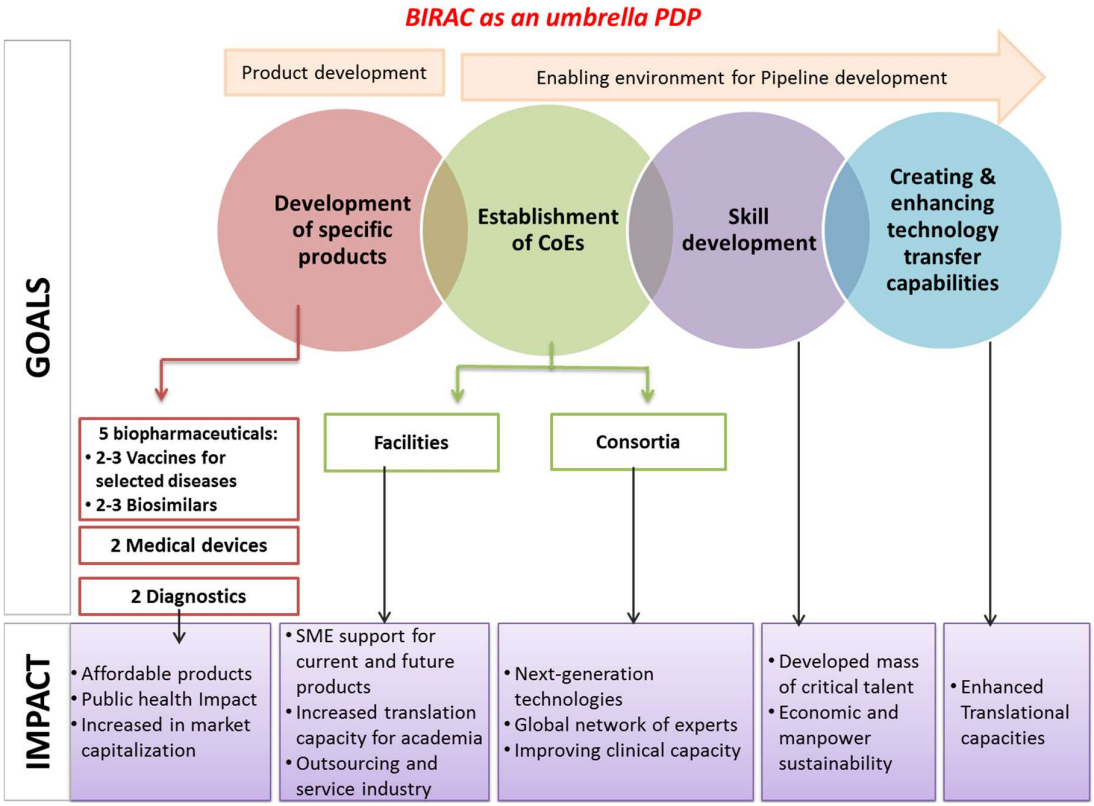
The program would facilitate skill development in vital areas of skills gap towards building an effective workforce and next generation leaders in following areas:

- Technical skill (e.g. next generation skills like genomics, NGS, Proteomics, high throughput screening, assay development, bioanalytical development, PK-PD studies etc.)
- Non-technical skill (e.g. technology transfer and licensing, compliance in GLP, GMP and GCP norms, regulatory knowledge, IP reading and legal expertise, project management and business development etc.)

iv. Creating and enhancing technology transfer capabilities in public and private sector including Intellectual Property Management:

The program would enhance academia-industry interlinking and provide increased opportunities for academia to translate knowledge into products and technologies through the following activities:

- Setup of Technology transfer offices;
- Training of technology transfer and Intellectual Property Management professionals;
- Providing assistance for acquisition and adaptation of technologies.



1.1.4 IMPLEMENTATION MODALITY

The Mission Programme of Department of Biotechnology, Ministry of Science & Technology will be implemented by Biotechnology Industry Research Assistance Council a Public Sector Undertaking of the Department. For this a Programme Management Unit will be set up at BIRAC which has the experience of managing the Department of Biotechnology (DBT) - Bill & Melinda Gates Foundation (BMGF) partnership and based on its excellent performance and strength Wellcome Trust and U.S. Agency for International Development (USAID) have also now joined as its partner. For the implementation of various components public and private sector researchers, institutes and industries, start ups and entrepreneurs would be supported who will be selected through a competitive system based on defined selection criteria.

Biotechnology Industry Research Assistance Council (BIRAC) was set up by the Department of Biotechnology to act as an interface to serve emerging biotech industries. Its core philosophy is to foster innovation by enabling biotech start-ups in translating innovative research to affordable and need based technologies and products with the purpose of catalyzing innovation driven biotech enterprise and create a true "Indian Bio-economy". BIRAC has so far supported nearly 500 Biotech companies and public sector researchers including start ups and entrepreneurs. Nearly 50 products and technologies are at an advanced stage of development and over 100 new IP have been generated. These schemes and the leads from these will be the basis of further study and research under the Mission. BIRAC being well-woven into the basic, clinical and translational research networks in the country; makes it relevant that the proposed Mission Program be structured to function in a PDP mode. BIRAC playing the central role *as a PDP* would be responsible for bringing together partners through existing frameworks for specific programmatic goals and would facilitate this program by:

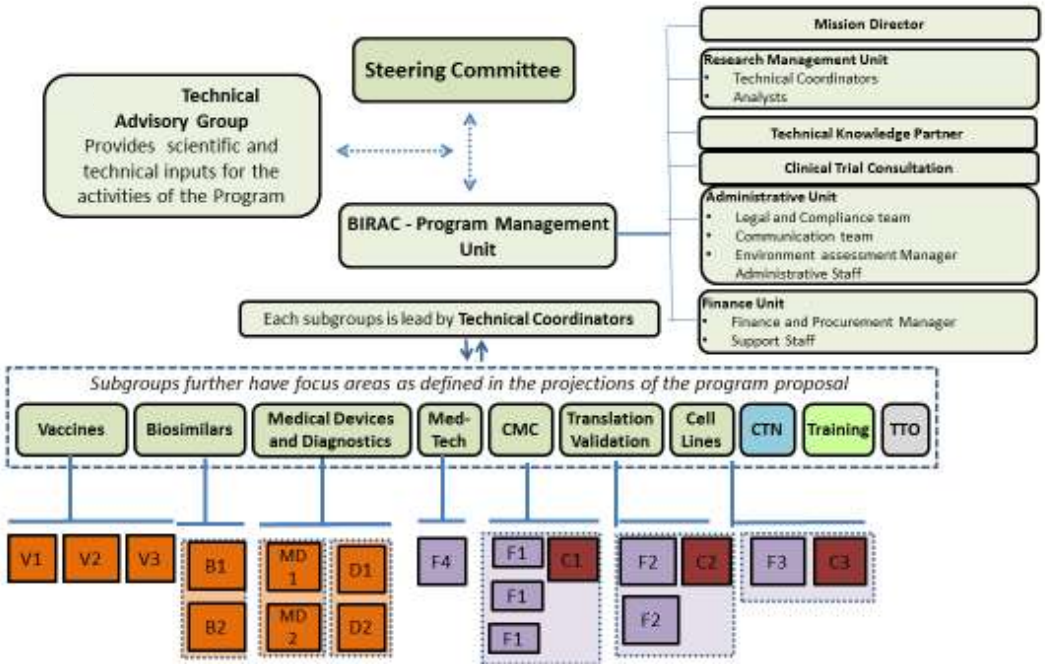
- Engaging with multiple partners (in-country & global network of research entities) and aligning their goals with the common interest;
- Providing access to experts/mentor/advisors (global and Indian) at different stages of product development;
- Utilization existing indigenous potential, resources and infrastructure;
- Development of technical and non-technical skills for product innovation;
- Ensuring next-generation technology acquisition and adaptation;
- Building a non-competitive environment promoting industry-academia collaboration accelerating translational research;
- Engaging with regulatory authorities;
- Safeguarding IPR and technology management policies for all the parties involved.

Efficient conduct of the program could be further facilitated by involving established organization(s) with relevant expertise in product development to act as the Product

Development Management arm for the PMU, supported by the Research Management Team consisting of Technical Coordinators and Analysts; the Administrative Unit consisting of legal and compliance personnel, communications team, environment assessment manager and other administrative staff; and a Finance Unit comprising of financial and procurement manager.

The PMU will also engage Technical Knowledge Partner to provide assistance for technical consultations and for preparing scientific documents to facilitate Scientific and Technical Advisory Committee in decision making.

A Clinical Trial consultant will also be engaged for all Clinical Trial activity guidance and oversight.



1.2 RATIONALE FOR CRVMF

Though DBT and BIRAC's effort are helpful in bridging some funding gaps in product development, the need for translational research in the current ecosystem is still significant. Product-oriented discovery and translational research in the country can be enabled by enabling shifting of focus on intensive validation and early proof–of-concept development; aiding synergy of innovation and commercialization through accessible and affordable development (i.e., discovery validation and bio-manufacturing) facilities; adapting new global innovations

and technologies; promoting advancement of tools and platforms technologies across the entire biopharmaceutical product development value chain, adopting global best practices in product non-clinical and clinical validation and strengthening domain specific skills for bridging human resource gaps including competency in the area of regulatory dossier development. The impact of various components have been discussed in PIM.

Clinical Trial (CT) Risk Management

Insights in social impact assessment in connection to CT are based on the elements given below;

- Protocol design
- Social value
- Scientific validity
- Nature of trial participants
- Fair subject selection
- Respect for human subjects
- Favourable risk-benefit ratio
- Investigator responsibilities
- Full and informed consent
- Costs and reimbursements
- Breach of confidentiality and protocol violations
- Compensation and Insurance
- Post- trial access issues
- Audit and Independent review

Based on the above assessment a framework for managing the risks under the programme is hereby proposed.

1.3 REPORT STRUCTURE OF CRVMF

The present report on CRVMF is structured in a manner that will cover the essential aspects of the environmental elements pertinent to the programme.

Section 2 covers the Legal and Regulatory Requirement where national and global guidelines, clinical trial requirements and the social safeguard policies of World Bank are mentioned. Section 3 encompasses the Management Framework proposed at various levels under the Program and means of implementation. Section 4 appertains to the World Bank mandate and grievance redressal mechanism specifically determined for the Program. Section 5 is about the Capacity building activities and the technical assistance. Section 6 is Summary and Conclusion.

2. LEGAL AND REGULATORY REQUIREMENT

2.1 STANDARD PRACTICES IN INDIA

Indian Framework

The Indian regulatory pathway has been well defined involving multiple agencies across ministries depending on the function and complexity of the biopharmaceutical.

The ethical issues faced by the pharmaceutical or biotechnology industry under the Programme are manifest in human participant trials; animal testing and handling of biological samples

Bioethics management approaches include: Well established ethics mechanisms including management commitment; dedicated internal ethics personnel; access and use of external expertise (e.g. consultants and advisory boards); internal training and accountability mechanisms; communications programs to engage with suppliers and external stakeholders; and evaluation and reporting mechanisms in all stages of research and development as stated hereunder;

Any 'intervention' – be it a product, procedure or health care system in order to improve standard of care will undergo preclinical and clinical trial process.

2.1.1 PRECLINICAL STEPS

Preclinical steps include: getting idea for drug target, developing a bioassay, screening the lead compounds in assay, establish effective and toxic amounts through *in vitro* studies and animal studies and file for approval as an Investigational New Drug to conduct clinical trials.

Experimentation on animals in course of medical research and education is covered by provisions of the Prevention of Cruelty to Animals Act, 1960 and Breeding of and Experiments on Animals (Control & Supervision) Rules of 1998, 2001 and 2006 framed under the Act. These are enforced by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), a statutory body. Under the Rules, in 2006, powers to permit experiments on small animals were given to Institutional Animal Ethics Committee (IAEC) of the establishments. Only proposals for conducting experiments on large animals are required to be sent to CPCSEA for approval. Indian National Science Academy (INSA) "Guidelines for care and use of animals in scientific research", revised in 2001for-

1. housing, care, breeding and maintenance of experimental animals to keep them in physical comfort and good health and to permit them to grow, reproduce and behave normally;

2. sources of experimental animals of known genetic, health and nutritional status;

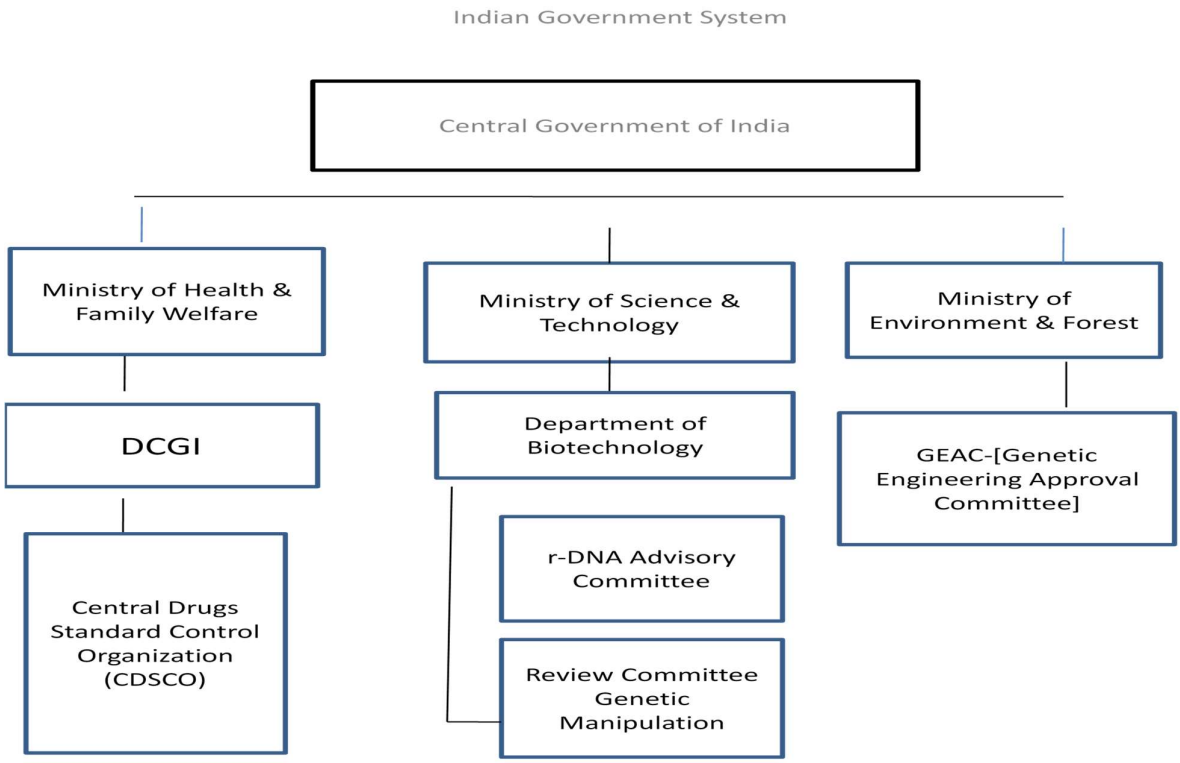
3. development of training facilities for scientists, technicians and other supportive staff for the care of animals and their use in experiments;

4. acceptable experimental techniques and procedures for anesthesia and euthanasia;
5. developing alternate in-vitro systems to replace animal experiments;
6. the constitution of institutional ethics committees, their functions and the legal and ethical obligations to ensure minimal and ethical use of animals

2.1.2 BACKGROUND INFORMATION ON CLINICAL TRIAL

The Drugs and Cosmetics Act in 1940 (DCA) provides for the regulation of import, manufacture and sale and distribution of drugs. The central and the state governments are both identified as regulators under the DCA. Regulatory functions are clearly separated between these two primary regulators.

The various agencies under the Central Government involved in the drug regulation have been shown in the following figure.



The Central Drugs Standard Control Organization (CDSCO) headed by the Drug Controller General of India (DCGI) is the main regulatory authority for pharmaceutical products and medical devices, and works under the MoHFW. The CDSCO is responsible for:

- include approval of new drugs
- registration and control of imported drugs
- approvals for clinical trials
- laying down standards for drugs, cosmetics, diagnostics and devices
- approval of licenses for high risk products (large volume parenteral, vaccines and biotechnology products and operation of blood banks)
- coordinating activities of the states and advising them on matters of uniformity in regulatory administration in the implementation of the DCA

Other advisory bodies that are under the CDSCO are:

- SEC and MDAC - panels set up to advise in matters related to review and regulatory approval of clinical trials and new drugs, except for Investigational New Drugs (INDs), relating to different (12) therapeutic areas for Subject Expert Committee (SEC) formerly called as NDAC and 07 MDAC.
- Technical Review committee (TRC) shall review the recommendations provided by SEC on applications of clinical trials and new drugs after thorough evaluation. DCGI will grant approval of clinical trial and new drugs based on recommendations of TRC.
- CLAA - Central Licenses Approving Authority. The CLAA is a branch of the CDSCO, will serve as the main regulatory body for medical devices. The CLAA will classify medical devices. In consultation with an expert panel on medical devices, the CLAA also will set and enforce safety standards, appoint notified bodies to oversee conformity assessment, conduct post-market surveillance, and issue warnings and recalls for adverse events. The CLAA follows the Bureau of Indian Statistics (BIS) and International Organization for Standardization (ISO) specifications for assessing medical devices.
- Drugs Technical Advisory Board (DTAB) - DTAB acts as a primary forum for rulemaking, but it is an advisory body and, therefore, can only make recommendations to the CDSCO.

At the state level the State Drug Controller (SDC) heads the State Drug Regulatory Authorities (SDRA) and reports to a joint secretary in the health department of state governments. The state authority is primarily concerned with:

- licensing of manufacturing establishments and sale premises and ensuring compliance with license conditions

- testing and monitoring of quality of drugs
- Sales and distribution of drugs in the state in question.

In addition to the above, six competent authorities and their composition are as follows:

i. Recombinant DNA Advisory Committee (RDAC) – advisory function

ii. Institutional Biosafety Committees (IBSC) – under the Department of Biotechnology (DBT)

iii. Review Committee on Genetic Manipulation (RCGM) - under the Department of Biotechnology (DBT)

iv. Genetic Engineering Approval Committee (GEAC) - Under the Ministry of Environment and Forest

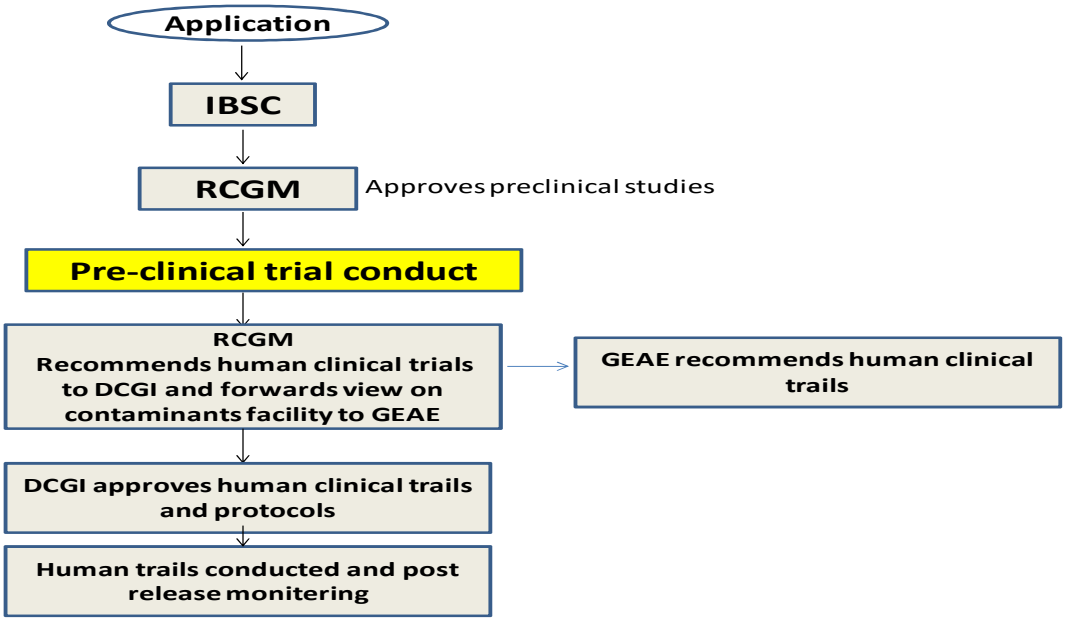
v. State Biosafety Coordination Committees (SBCC)

vi. District Level Committees (DLC).

While the RDAC is advisory in function, the IBSC, RCGM, and GEAC are of regulatory function. SBCC and DLC are for monitoring purposes. Three tier mechanism comprising Institutional Biosafety Committees (IBSC) at the Institute/ company; the Review Committee on Genetic Manipulation (RCGM) in the Department of Biotechnology; and the Genetic Engineering Approval Committee (GEAC) in the Ministry of Environment & Forests (MoE&F) for granting approval for research and development activities on recombinant DNA products, environmental release of genetically engineered (GE)crops and monitoring and evaluation of research activities involving recombinant DNA technology has been established.

Regulatory Authority	**Clearance stage in the project**	**Requirements**
Institutional Bio Safety Committee (IBSC) for all the Research activities related to rDNA technology	▪ Managing infectious agents and/or regulated GMOs/LMOs/rDNA material in the laboratory scale where they are being handled or maintained ▪ To ensure bio safety on-site	▪ IBSC shall be registered for a period of three years. ▪ IBSC can simply note the information provided by PI, give permission before start of the experiments or forward it to RCGM for approval as per the Recombinant DNA Safety Guidelines, 1990 of DBT

Review Committee on Genetic Manipulation (RCGM), (RCGM is the Regulatory Authority functioning in DBT to whom IBSCs shall report and Genetic Engineering Appraisal Committee (GEAC) is the apex Regulatory Authority functioning in MoEF responsible for authorizing environmental release).	▪ For all pre-clinical studies and field trials and large scale production (in-vitro or in-vivo physiological, toxicological and efficacious potential of r-DNA product prior to initiation of human studies) ▪ Any exchange of genetically engineered cell bank. ▪ GMOs/LMOs/rDNA material in the large scale (more than 20 liters).	▪ Institutional Bio Safety Committee (IBSC) ▪ Institutional Animal Ethics Committee (IAEC), ▪ GLP certification of proposed facility
Genetic Engineering Appraisal Committee (GEAC) under Ministry of Environment and Forests (MoEF)	▪ For activities where final drug product contains genetically modified organisms/ living modified organisms(Ex- DNA vaccines) ▪ Activities involving large scale use of hazardous microorganisms and recombinants . ▪ Activities related to release of genetically engineered organisms and products into the environment. ▪ Field trials	RCGM and IBSE clearance.



The registration of the clinical trial with the Clinical Trials Registry-India (CTRI), has been made mandatory by the DCGI has since 15th June 2009. Registration of the trial with CTRI involves declaration and identification of trial investigators, sponsors, interventions, patient population etc before the enrollment of the first patient in the clinical trial.

2.2 CURRENT REGULATORY AND CLINICAL TRIAL PATHWAY FOR BIOPHARMACEUTICALS

For vaccines and other biopharmaceuticals, the following regulatory activities and the concerned authorities have been tabulated below.

	Regulatory Activity	Authorities
Preclinical	• Review of experimental facilities ensuring safety measure • Approval for pre-clinical animal studies	• Institutional Biosafety Committees (IBSC) – approval of the project in terms of biosafety and recommends it to RCGM • Review Committees on Genetics Manipulation (RC GM)
Clinical	• Preclinical data evaluation for clinical trials	• CDSCO – relies on expert committees.

	• Applications online in the Clinical Trials Registry – India (CTRI) • Good Clinical Practices • Registration of Ethics Committee • Serious Adverse Events (SAE) reporting •	• Phase 3 clinical trials are approved after consultation with GEAC • Institution Ethics Committee
Large Scale manufacturing	• License to manufacture • Inspiration of Good Manufacturing Practices • Facility inspection	• State Drug Regulatory Authorities (SDRA) for licensing and facility inspection
Delivery/Market	• Application for License to distribute sell	• State Drug Regulatory Authorities (SDRA) •
Post market Surveillance	• Periodic Safety Update Reports (PSURS) • Adverse Drugs Monitoring	• CDSCO for PSURS • Indian Pharmacopoeia Commission for Adverse Drug Monitoring Centre (AMCs)

WP (civil) 33/2012 of Swasthya Adhikar Manch and another Vs Ministry of Health and Family Welfare and Others is the pivotal court case before the Supreme Court of India that yielded numerous Guidelines with regard to the Clinical Trial Process. All the observations of the apex court have taken shape of relevant Guidelines that are required to be complied with by sponsors and implementers of the Clinical Trial. The various guidelines for registration of the Institutional Ethics Committee, Serious Adverse Event Reporting, Compensation, monitoring and audit etc. are available in the CDSCO website and in general public domain. The Compensation guidelines as prescribed are provided hereunder;

1. Formula to Determine the quantum of compensation in the cases of Clinical Trial related serious Adverse Events(SAEs) of Injury other than Deaths Occuring During Clinical Trials **(for details please see Annexure 1)**
2. Formula to Determine the quantum of compensation in the cases of Clinical Trial related serious Adverse Events(SAEs) of Deaths Occurring During Clinical Trials **(for details please see Annexure 2)**

2.2.1 CLINICAL TRIAL APPROVAL PROCESS

A Clinical Trials can only be initiated after obtaining written permission from Institutional Ethics Committees (IEC) and DCGI

2.2.1.a. Approval from CDSCO/DCGI:

Applications of clinical trials and new drugs will initially be evaluated by the SECs Subject Experts Committee (SEC, formally known as New Drugs Advisory Committee) SEC acts as a gateway in the clinical trial approval process by advising the DCGI. Currently 16 committees are formed.

Recommendations from SEC will be reviewed by Technical Review Committee (TRC). The TRC is proposed to be constituted under DGHS consisting of experts from each areas like clinical pharmacology, regulatory clinical toxicology/pathology, medicinal/pharmaceutical chemistry, pharmacy and immunology including clinicians, basic scientists, involved in drug development and subjects specialists (drug indication-wise).

CDSCO will grant approval of clinical trials and new drugs based on the recommendations of TRC. CDSCO/DCGI provides clearance to clinical trials only on the condition that they will be reviewed and certified by an IEC.

2.2.1.b. Approval from IEC:

The protocol must be reviewed and approved by an IEC.

Composition of IEC

IECs should be multidisciplinary and multisectorial in composition. Independence and competence are the two hallmarks of an IEC. The number of persons in an ethical committee should be kept fairly small (7-9 members). It is generally accepted that a minimum of five persons is required to compose a quorum.

The Chairperson of the Committee should preferably be from outside the Institution and not head of the same Institution to maintain the independence of the Committee. The Member Secretary who generally belongs to the same Institution should conduct the business of the Committee. Other members should be a mix of medical / non-medical scientific and non-scientific persons including lay public to reflect the differed viewpoints. The composition may be as follows

1. Chairperson
2. 1-2 basic medical scientists.
3. 1-2 clinicians from various Institutes
4. One legal expert or retired judge
5. One social scientist / representative of non-governmental voluntary agency
6. One philosopher / ethicist / theologian
7. One lay person from the community
8. Member-Secretary

The ethical committee at any institution can have as its members, individuals from other institutions or communities if required. If required, subject experts could be invited to offer their views, for example for drug trials a pharmacologist, preferably a clinical pharmacologist, should be included. Similarly, based on the requirement of research area, for example HIV, genetic disorders etc. specific patient groups may also be represented in the Committee. The membership of IEC will include Epidemiologist(s), Sociologist(s), Lawyer(s), Theologian, Statistician(s), Clinician(s), Basic scientists, Pharmacist(s)/Clinical Pharmacologist(s) etc They should be appointed by the Head of the Institute based on their competencies and integrity, and could be drawn from any public or private Institute from anywhere in the country.

IEC should be constituted in the following pattern:

i) A Chairperson
ii) A Deputy Chairman if need be,
iii) A Member Secretary,
iv) 5-15 members from different Departments / Specialties / disciplines or areas etc.

Application Procedures:

All proposals should be submitted in the prescribed application form, the details of which are as follows

For a thorough and complete review, all research proposals should be submitted with the following documents:

1. Name of the applicant with designation

2. Name of the Institute/ Hospital / Field area where research will be conducted.

3. Approval of the Head of the Department / Institution

4. Protocol of the proposed research

5. Ethical issues in the study and plans to address these issues.

6. Proposal should be submitted with all relevant enclosures like proformae, case report forms, questionnaires, follow - up cards, etc.

7. Informed consent process, including patient information sheet and informed consent form in local language(s).

8. For any drug / device trial, all relevant pre-clinical animal data and clinical trial data from other centres within the country / countries, if available.

9. Curriculum vitae of all the investigators with relevant publications in last five years.

10. Any regulatory clearances required.

11. Source of funding and financial requirements for the project.

12. Other financial issues including those related to insurance

13. An agreement to report only Serious Adverse Events (SAE) to IEC.

14. Statement of conflicts of interest, if any.

15. Agreement to comply with the relevant national and applicable international guidelines.

16. A statement describing any compensation for study participation (including expenses and access to medical care) to be given to research participants; a description of the arrangements for indemnity, if applicable (in study-related injuries); a description of the arrangements for insurance coverage for research participants, if applicable; all significant previous decisions(e.g., those leading to a negative decision or modified protocol) by other ECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of the modification(s) to the protocol made on that account. The reasons for negative decisions should be provided.

17. Plans for publication of results – positive or negative- while maintaining the privacy and confidentiality of the study participants.

18. Any other information relevant to the study.

Review procedures:

a. The meeting of the IEC should be held on scheduled intervals as prescribed and additional meetings may be held as and when the proposals are received for review.
b. The proposals will be sent to members at least 2 weeks in advance.
c. Decisions will be taken by consensus after discussions, and whenever needed voting will be done.
d. Researchers will be invited to offer clarifications if need be.
e. Independent consultants/Experts will be invited to offer their opinion on specific research proposals if needed.
f. The decisions will be minuted and Chairperson's approval taken in writing.

Elements of review

a. Scientific design and conduct of the study.

b. Approval of appropriate scientific review committees.

c. Examination of predictable risks/harms.

d. Examination of potential benefits.

e. Procedure for selection of subjects in methodology including inclusion/ exclusion, withdrawal criteria and other issues like advertisement details.

f. Management of research related injuries, adverse events.

g. Compensation provisions (relating to physical injury).

h. Justification for placebo in control arm, if any.

i. Availability of products after the study, if applicable.

j. Patient information sheet and informed consent form in local language.

k. Protection of privacy and confidentiality.

l. Involvement of the community, wherever necessary.

m. Plans for data analysis and reporting

n. Adherence to all regulatory requirements and applicable guidelines

o. Competence of investigators, research and supporting staff

p. Facilities and infrastructure of study sites

q. Criteria for withdrawal of patients, suspending or terminating the study

Decision-making

a. Members will discuss the various issues before arriving at a consensus decision. b. A member should withdraw from the meeting during the decision procedure concerning an application where a conflict of interest arises and this should be indicated to the chairperson prior to the review of the application and recorded in the minutes.

c. Decisions will be made only in meetings where quorum is complete.

d. Only members can make the decision. The expert consultants will only offer their opinions.

e. Decision may be to approve, reject or revise the proposals. Specific suggestions for modifications and reasons for rejection should be given.

f. In cases of conditional decisions, clear suggestions for revision and the procedure for having the application re-reviewed should be specified.

g. Modified proposals may be reviewed by an expedited review through identified members.

h. Procedures for appeal by the researchers should be clearly defined.

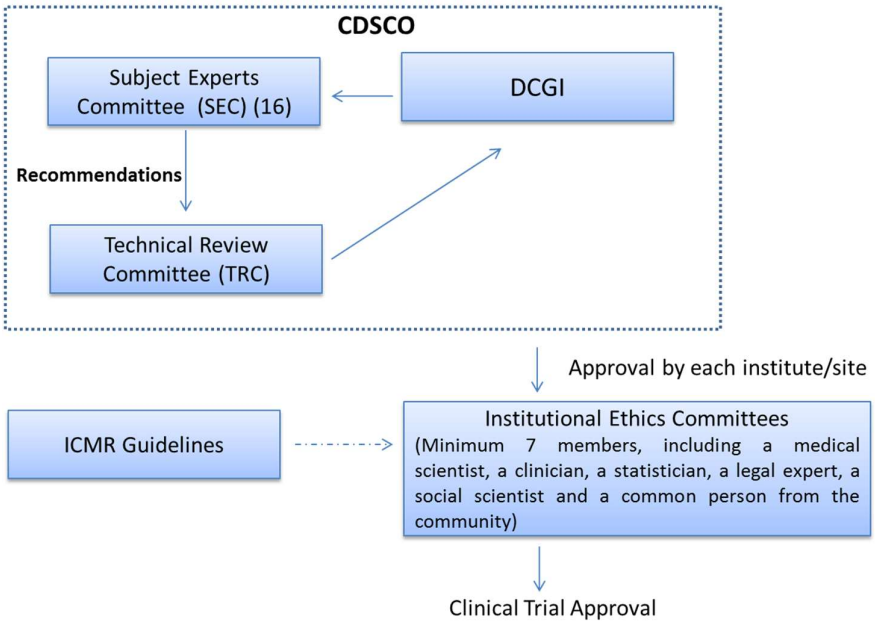
Communicating the decision

a. Decisions will be communicated by the Member Secretary in writing.

b. Suggestions for modifications, if any, should be sent by IEC.

c. Reasons for rejection should be informed to the researchers.

d. The schedule / plan of ongoing review by the IEC should be communicated to the PI.



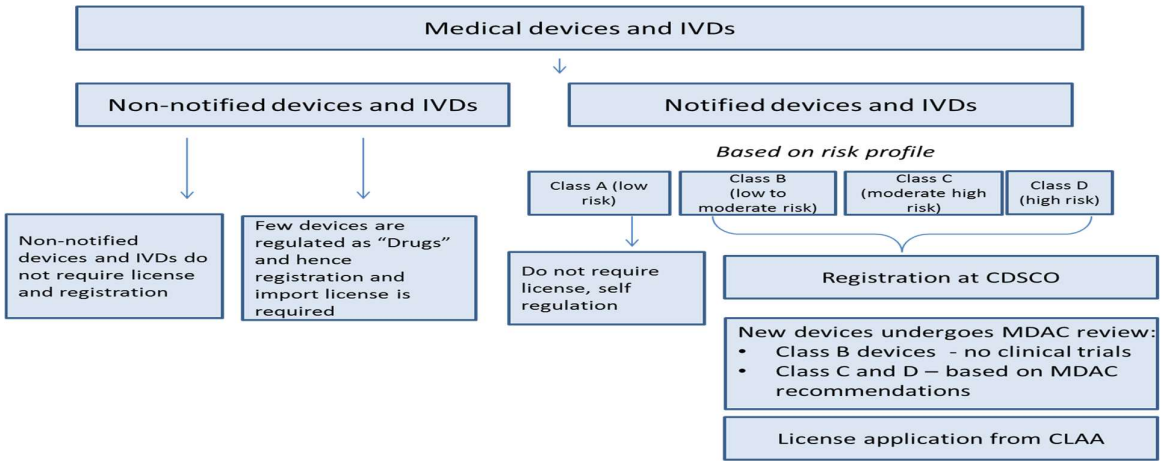
2.2.2 CONDITIONS UNDER WHICH CLINICAL TRIALS MAY BE WAIVED OFF

As per the GoI guidelines, "The waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside India, can be considered only in cases of "national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy".

In case of biosimilar development, a reduction in data requirements is possible for preclinical and /or clinical components of the development program by demonstration of comparability of product (similarity to authorized reference biologic) and the consistency in production process, which may vary depending on the characteristics of the already authorized reference biologic.

2.2.3 CURRENT MEDICAL DEVICE REGULATORY PATHWAY

Medical devices currently come under the umbrella of India's Drugs and Cosmetics Act and is regulated by the same rules as for pharmaceuticals.



- Only notified medical devices are regulated in India**. (details in the Annexure 3)**
- Registration is not required for import of non-notified medical devices in India. However, the few devices are regulated as "Drugs" under Drugs and Cosmetics Act and Rules, hence registration and import license is required for import in to India. **(details in the Annexure 4)**
- Class A devices do not require license and such devices are self-regulated in accordance with the applicable standards.
- For Class B, C and D devices, the CLAA, in consultation with the BIS, will publish a list of notified bodies authorized to perform conformity assessment. Medical device manufacturers must submit an application for assessment to one of these notified bodies. The necessary application materials will include technical documentation, corrective and preventative action procedures, as well as information about the organization and goals of the business.
- In the case of Class C and D devices, further information and clinical investigation may be required.

Clinical Trial Approval Process – for "New" medical devices

Notified medical devices (For Class C and D) for which predicate devices are not registered in India are classified as "new" medical devices. These medical devices are referred to the Medical Device Advisory Committees (MDAC) to comment on safety, effectiveness, essentiality and desirability of proposed New Devices.

Currently, Medical Device Advisory Committees cover the following specialties – Cardiovascular, Dental, Ophthalmic, Orthopedic, Reproductive and Urology and a miscellaneous devices committee. Further, the CDSCO has also formulated a "General Expert Pool" for Medical Device Advisory Committee to advise the Drugs Controller General of India in matters related to review and regulatory approval of new medical devices and clinical trials.

2.2.4 GUIDELINES FOR QUALITY MANAGEMENT

Good Laboratory Practices (GLP) are to ensure a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

Good Participatory Practices (GPP) for vaccine clinical trials will be ensured in order to have effective partnerships between research teams and stakeholders. GPP is to be adhered to in the "design and conduct of biomedical vaccine trials" refers to activities required for the development, planning, implementation, and conclusion of a trial, including dissemination of trial results. Tools for monitoring engagement activities and data entry and standardized reporting form integral part of the GPP. Though the guidelines have been developed primarily for HIV trials, the basic principles are now widely accepted as applicable for any vaccine trial to ascertain community participation.

Good Clinical Practices (GCP) refers to- "a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected." – Definition of ICH GCP. Unlike the GCP, which deals with the trial data integrity, the GPP provides guidance about the relationship between a trial's funders, sponsors, and implementers, and other stakeholders.

Good Manufacturing Processes is the part of quality assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by the Marketing Authorization or product specification thus concerned with both production and quality control. These manufacturing practices are designed to ensure the safety, identity, strength, quality, and purity of such drugs, devices and biologicals through setting standards for-

Documentation/Records
Process and production controls
Physical plant, laboratory, and facility design
Personnel / Quality control oversight
Proper validation of processes
Maintain and calibrate equipment
Materials Management

Packaging & Labeling
Storage & Distribution

Good Pharmacovigilance Practices (GVP) is another set of guidelines now prescribed by all global regulatory agencies in order to focus on premarketing and post marketing risk assessment, that is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.

Medical and related research using human beings as research participants will necessarily ensure that all the relevant laws and regulations including the guidelines of ICMR.

The following principles will be taken into account while assessing the proposal and while monitoring the implementation:

a. Principles of essentiality -whereby, the research entailing the use of human subjects is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research.

b. Principles of voluntariness, informed consent and community agreement- whereby, Study Subjects are fully apprised of the Study and the impact and risk of such Study on the Study Subjects and others; and whereby the research subjects retain the right to abstain from further participation in the research.

c. Principles of non-exploitation -whereby as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition, or status, or literacy, or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research.

d. Principles of privacy and confidentiality -whereby, the identity and records of the human subjects of the research or experiment are as far as possible kept confidential; and that no details about identity of said human subjects, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons.

e. Principles of precaution and risk minimization- whereby due care and caution is taken at all stages of the research and experiment.

f. Principles of professional competence -whereby, the research is conducted at all times by competent and qualified persons.

g. Principles of accountability and transparency -whereby, the research or experiment will be conducted in a fair, honest, impartial and transparent manner

h. Principles of the maximisation of the public interest and of distributive justice -whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind.

i. Principles of institutional arrangements -whereby, there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner.

j. Principles of public domain -whereby, the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications.

k. Principles of totality of responsibility -whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment.

3. MANAGEMENT FRAMEWORK

3.1 BIRAC OVERSIGHT FOR CLINICAL TRIAL MANAGEMENT

3.1.1 PRE SANCTION

In order to evaluate the risk mitigation capacity, the request for the proposal including global trial components if any shall provide the pre requisite criteria. The proposal format should require that the applicant should provide all the documents as true copy in connection to the approval/license/certificate for conduct of proposed activities of the project.

- Expert scrutiny for scientific and technical aspects including the

    1) Background/Significance,
    2) Study Design,
    3) Study Population,
    4) Risk Vs Benefit etc.
    5) Multicentric/global approach

- Quality Management (QM) personnel will be treated as the essential team evaluation criterion who will be responsible for the overall Clinical Trial process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control (QC), and quality assurance (QA) activities including the study specific CRVMF.

Following Information will be asked while submitting the proposal to BIRAC:

a. Rationale of the Study Supported by cited literature
b. Possible risk factors evaluated with details towards ensuring successful conduct of clinical trials
c. Full trial protocol with its appendices in the format that they plan to submit to the regulatory Aauthorise (as per ICH guidelines)
d. Available Non-Clinical And Clinical Information to support the proposed Clinical Trial
e. Copy Of Investigator Brochure
f. The Relevant Ethical Approvals Obtained (E.G. ETHICS COMMITTEES, DCGI ETC) including documentation on selection of subjects and ethical justification of involvement of vulnerable subjects.
g. IP Status

All documents submitted will be further evaluated.by external reviewer:

In all the Clinical Trial Projects, an expert from relevant agency such as the Clinical Development Services Agency (CDSA) will be integrated as the part of the BIRAC. The monitoring/auditing by the BIRAC covers all the five basic process of the clinical trial Projects:

1. Initiation
2. Planning
3. Execution
4. Data safety Monitoring and controlling deviations
5. Analysis and reporting

The proposed scrutiny and assessment system incorporates the following processes in order to prevent any adverse social impact. It involves a careful identification and definition of factors that have potential predictive value for noncompliance at the program level, the study level and the site investigator level. Constitution of committees shall be duly undertaken by BIRAC for assessment and oversight of the Projects from the pre-grant stage to the completion of Project Duration.

- The pre grant assessment shall include clinical trial feasibility aspect based on --clinical and epidemiological information, study design, investigational product, national relevance, investigator's readiness and the local demographics.
- Trial specific assessment by the domain experts shall depend on the therapeutic area, and proposed phase of study which will include status evaluation of existing treatment or alternative drugs, availability of standard care, inclusion and exclusion criteria, recruitment strategies and ensuring that the patient recruitment is consistent with the study design including other study specific procedures to identify evaluable patients.

- The Project monitoring Committee for every specific Clinical Trial shall have adequate oversight powers related to regulatory compliance including CT audits, export of biological materials, special requirements in case of biological samples, randomisation and blinding procedure, best practices for patient and public involvement (PPI), adequacy of insurance coverage throughout the study, protocol amendment or termination of study.
- The governing Clauses in the funding agreement shall encompass the propriety of informed consent process.

The method prescribed for consent, assent and permission shall include;

- Evaluation of existing knowledge of the participants
- Adoption of sound medical communication exercise including education and provision of information about all the details of the study and the subjects' rights.
- Validation of vernacular Informed consent document should be carried out independently.
- Specific aspects of protection related to the vulnerable populations that refers to but not limited to children, minors, pregnant women, fetuses, human in vitro fertilization, prisoners, employees, military persons and students in hierarchical organizations, terminally ill, comatose, physically and intellectually challenged individuals, institutionalized, elderly individuals, visual or hearing impaired, ethnic minorities, refugees, international research, economically and educationally disabled and healthy volunteers.[Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Participants, New Delhi, 2006]
- Re- consent on changes in benefit to risk ratios, either risks other than those assumed or a decrease in direct benefits presaged to the participant or both should result in a consideration of suspending further enrolment or discontinuation of further participation until the issue is appropriately corrected.
- Wherever required usage of audio-visual and illustrative tools to enhance quality of consent process shall be included
- The informed consent document (ICD) should also comply with local regulatory norms and the language and literacy capabilities of the participants
  In the circumstances where no pertinent investigational product information is available regarding unknown or probable fetotoxic or materno-toxic effects, it should be disclosed in the ICD.
- Age-appropriate assent forms must be developed for pediatric and adolescent subjects; permission forms must be developed for their parents or legal guardians.

Development of comprehensive safety monitoring plans with a review by Data Safety Monitoring Board (DSMB) shall be a mandatory requirement for all CTs and wherever applicable Observational Study supervision set ups shall be established.

Appropriate undertakings for the conduct of CT shall be submitted by the Sponsor and the investigator to BIRAC. The Sponsor should agree to provide compensation for any physical injury for which subjects are entitled to compensation through adequate insurance against risks to cover compensation, independent of proof of fault.

3.1.2 POST SANCTION

The funding agreement would also provide necessary governing conditions to ascertain compliance with the requirements etc. Specifically, the agreement shall have indemnification clause and primary responsibility clause, dispute resolution clause, including the termination in the event of breach clause.

The Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) will be put in place as an independent group of experts to assess the performance of overall study operations and any other relevant issues of each Product Development Unit (PDU). Not all clinical trials require DSMBs; for some a simpler approach will suffice. The monitoring as necessary will include;

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness;
- Performance of individual trial sites;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

Recommendations regarding modification of the design and conduct of the study will be considered by SAG based on:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance or rate of enrolment;
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines;
- Suspension or early termination of the study based on the results of a futility analysis indicating a very low probability of finding a statistically significant resultwith regard to theprimary outcome measure.

The technical coordinator from the PMU shall not be part of the DSMB, but shall be part of the comprehensive safety monitoring of the Project including the review of DSMB reports and the milestone performance.

The constitution of DSMB members depending on the phase of the trial, range of medical issues, complexity in design and analysis, and potential level of risk shall include:

1. Expert(s) in the clinical aspects of the disease/patient population being studied;
2. One or more biostatisticians; and,
3. One or more investigators with expertise in current clinical trials conduct and methodology including ethical considerations.

PMU level

The PMU shall have the following monitoring components under the Programme-

- Team Qualifications and Agreements
- committed Resources
- Medical Care of Trial Subjects
- Ethical clearance
- Compliance with ethical approval terms
- Adherence to conditions related to investigational product
- Randomization Procedures and Unblinding
- Informed consent and recruitment process
- Protocol deviations
- Records and Reports as per the regulations
- Data Safety Monitoring board reports
- Half yearly progress report of the Project and site visit
- Safety reporting and Premature Termination or Suspension of Trial
- Issues related to compensation
- Completion site visit
- Post-trial access to the investigational product

Implementation of this CRVMF shall be facilitated through the designated Technical Coordinator of the PMU with the help of external Consultant or Consultancy Firm under the I-3 Programme.

PDU level

Every PDU under the Program will constitute a core committee having a designated person for implementation of this CRVMF from among the investigators including the QM person. The quarterly Project report shall have a separate compliance status on CRVMF.

3.2 PUBLIC DISCLOSURE REQUIREMENTS

Every fund recipient shall be required to put in their websites the project summary and expected deliverables. The study results shall be managed in such a way to insure the global access. The

BIRAC website should also provide project summary & related non-confidential elements of project. The governing agreement shall have a provision to secure adequate sharing of basic data/documentation /subject/master sheet/periodic reports etc during project monitoring and carried out by project monitoring committee.

Apart from this, BIRAC as well as fund recipient shall disclose any other statutory disclosure that is under prevailing regulation as well as aspects of project implementation.

The PMU will disclose the CRVMF at three levels:

- At the level of BIRAC;
- At the level of DBT and
- At the level of World Bank.

The CRVMF will be uploaded in the website of DBT and BIRAC in English and in Hindi as the Programme covers a number of States in India.

At the level of the World Bank, the Bank will disclose this CRVMF as per norms.

3.3 INFORMED CONSENT

The process of Informed Consent is very important for any Clinical Trial conduct and the following aspects will be considered under the Programme;

Basic elements of informed consent that will be ensured in the format

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects involved in the study.

Process to be ascertained After Consenting/Assenting

- copy of the signed consent/assent document to the subject and/or parent/legal guardian to be given.
- original to be retained and updated in the study enrollment or screening log.

Documenting The Consent/Assent Process To be ensured

The informed consent/assent process should be documented, to include key details of the process including;

Essential	Date and time the consent/assent was obtained.
Essential	The subject/participant read/understands the consent document.
Essential	All questions were answered and risks were reviewed.
Essential	The subject, or his/her legally authorized representative, personally signed and dated the document and received a copy.
Essential	No study-related procedures were initiated prior to obtaining a signed consent document.
Additional	Ample time was allowed for review and discussion.
Additional	The version of the consent/assent document that was signed.
Additional	The witness, if used, and person obtaining consent have signed and dated the document, if applicable.
As applicable	Special issues, such as non-English speaking subjects, were appropriately addressed.

Re-Consenting requirements

- Follow IRB guidelines regarding the need to re-consent subjects/participants in the event of an updated and IRB-approved consent/assent document, if no significant changes are made to the risk profile or procedures associated with the study.
- If changes are made to the protocol that may affect the subject's willingness to continue participating in the study, subjects/participants must be re-consented.
- Minor subjects/participants who signed an assent document and subsequently reach 18 years of age during study participation must then sign a consent document.

4. GRIEVANCE REDRESSAL

4.1 WORLD BANK MANDATE

Communities and individuals who believe that they are adversely affected by a World Bank (WB) supported project may submit complaints to existing project level grievance redress mechanisms of the WB's Grievance Redress Service (GRS). The GRS ensures that complaints received are promptly reviewed in order to address project related concerns. Project affected communities and individuals may submit their complaint to the WB's independent Inspection Panel which determines whether harm occurred, or could occur, as a result of WB non-compliance with its policies and procedures. Complaints may submitted at any time after concerns have been brought directly to the World Bank's attention, and Bank Management has been given an opportunity to respond. For information on how to submit complaints to the World Bank's corporate Grievance Redress Service (GRS), please visit http://www.worldbank.org/GRS.

4.2 PROGRAM BASED GRIEVANCE REDRESSAL MECHANISM

To strengthen the monitoring and risk mitigation BIRAC will develop a fabric of feedback including 'whistle blower' inputs. The process in its entirety will assure all information providers the confidentiality needed to encourage participation. Online and site specific Project platforms for anonymous contributions and reporting of incidents by the public, employees, data users, trial participants and other stakeholders shall be provided for. Guidelines for prompt actions on receipt of any suggestion or complaint shall be determined. Remedial measures accordingly shall be initiated as per the recommendation of specific committee constituted for this purpose.

Common Grievance mechanism to deal with the aspects of environmental, clinical trial, social and other complaints shall be put in place.

The following considerations shall be taken into account:

a. ***Who can file a complaint?***

The public, employees, data users, trial participants and other stakeholders of the I3 Programme.

b. ***Who can receive the complaint/concern?***

BIRAC website shall have the on-line information and the submission form with regard to any concern, dissatisfaction or complaint under the I3 Programme. The Head of the Administrative Unit of the BIRAC-PIU shall receive the submission.(through post or on-line or by hand).

c. ***Timeline/limitation for filing complaint***

The complaint shall be considered if the cause of action is claimed to have occurred within six months before filing the Complaint

d. ***Processing of the complaint***

An on-line submission system shall be developed at BIRAC to receive the complaints or concerns and an acknowledgement of receipt shall be sent within 48 hours of receipt of such submission. Simultaneously, the acknowledgement with a copy of the submission shall be sent to DBT and World Bank.

e. ***Timeline for dealing with the complaint***

The Committee having the PIU Director, Head of the Administrative Unit of the BIRAC-PIU and Head of the Technical Unit at BIRAC-PIU shall look into the submission and initiate the required investigation.

f. ***Decision and appeal mechanism***

The para wise reply to the submission should be prepared by the above committee. This reply shall be sent to the DBT and the World Bank and not to the entity submitting the concern or complaint. After due approval a single paragraph reply based on the presence of any substance or not shall be sent to the submitting entity within two weeks from the receipt of the Complaint or concern. If there is a material finding, immediate remedial measures shall be taken.

g. ***Appellant authority***

The submitting entity can file an appeal on the reply within two weeks from the date of the issue of the same by the BIRAC-PIU. The Appellate Authority shall be the Managing Director of BIRAC who shall look into the subject matter and pass a decision within two weeks from the date of receipt of such appeal.

h. ***No restriction on the legal rights to approach the court of law***

The present Grievance Redressal mechanism shall not be construed as restriction of any form to the legal right to approach the court of law in the absence of mutually agreed upon mechanism to Arbitrate, mediate or Conciliate.

i. ***Record preservation mechanism***

The submission, investigation documents, decisions and related information shall be preserve for at least five years from the date of the final decision in the corresponding matter.

Documentation of the Grievance Redress Mechanism

The mechanism of grievance redress will be a regular, transparent and participatory one and is an important and integral part of I-3, PMU's governance and social accountability agenda. A separate Case File for each grievance/complaint received in which all related documents and record of discussions will be kept in the form of the following three Registers;

► ***Complaints/Grievances Register*** *will* contain (a) Serial Number; (b) Case Number; (c) Name of the Grieved/Complainant; (d) Name of Father/Husband; (e) Gender (f) Age; (g) Full Address; (h) Brief details of grievance/complaint; (i) List of documents, if any, attached; (j) Details of previous grievance/complaint, if any; (k) Date of receipt of grievance/complaint and (l) Date of acknowledgement of grievance/complaint.

► ***Resolution Register*** will have details of (1) Serial Number; (2) Case Number; (3) Name of the Grieved/Complainant; (4) Details of grievance/complaint (5) Field visit, if any, and findings; (6) Date of public hearing; (7) GRC's decision; (8) Details of decisions – redressed, pending or rejected and (9) Agreement reached/Commitment made.

► ***Closing Register*** will contain details of (i) Serial Number; (ii) Case Number; (iii) Name of the Grieved/Complainant; (iv) Date of Hearing; (v) Decision– whether or not accepted; (viii) Date, medium and mode of communication to the grieved/complainant and (ix) Date of closing of grievance/complaint.

The Progress report of the I-3 programme will have the status component on the Grievance Redressal Mechanism.

5. CAPACITY BUILDING AND TECHNICAL ASSISTANCE

Required training with regard to CRVMF will be made as integral part of the broader training component and Setting up of the clinical trial units under the Programme. The relevant components are termed hereunder;

Building and strengthening domain specific knowledge and management skills	I. Skill development through international exposure in vital areas of skill gap II. Investment in existing training centers III. Content and courseware development that can be delivered by designated training partners

Training for CRVMF elements will be enabled through a separate module as part of the activities of skill developments and the setting up of the network of Clinical Trial Units.

Activity
Skill development through international exposure and designated training partners in vital areas of skill gap – (scientists, budding entrepreneurs, industry representatives)

• Areas of Skill development include-
  • Onsite training for validation skills (bioanalytical development, PK-PD studies, assay development etc)
  • Onsite training for biomanufacturing skills (upstream/downstream and quality assurance)
  • Training in other interdisciplinary areas required for development of new technologies (e.g. development of novel assays, manufacturing tools & technologies, and cell lines & expression systems)
  • Clinical trial capabilities on site
  • Compliance in GLP, GMP and GCP norms
  • Regulatory knowledge including EMF
  • Intellectual property reading and legal expertise
  • Onsite training in the area of technology transfer and licensing
  • Project management
  • Business development

5.1 POST SELECTION ORIENTATION PROGRAMMES FOR AWARENESS AND TRAINING ON CRVMF

BIRAC will provide hands on training as well as regulatory approval training to the fund recipients. The training will cover following activities:

- Technical skill (e.g. next generation skills like genomics, NGS, Proteomics, high throughput screening, assay development, bioanalytical development, PK-PD studies etc.)
- Non-technical skill (e.g. technology transfer and licensing, compliance in GLP, GMP and GCP norms, regulatory knowledge, IP reading and legal expertise, project management and business development etc.)

5.2 PERIODICAL TRAINING DURING THE PROGRAMME DURATION FOR CAPACITY BUILDING

- Key persons trained in technical skills and non-technical skills
- Bridging the talent gap in the ecosystem will enable efficient product development

- Interdisciplinary trainings would enable innovative thinking and cross learning
- Proficiency in intellectual property support and management
- Empowering next generation entrepreneurs by equipping them with management and business development skills

6. SUMMARY AND CONCLUSION

The present Framework has made efforts to consolidate the required management parameters as much as possible. But, it is a dynamic document that has to evolve as the Programme gets implemented and based on pragmatic considerations.

Annexure 1

File No: **CT/SAE-ND-COMPENSATJON FORMULAE/2014**

GOVERNMENT OF INDIA

Ministry of Health & Family Welfare
Directorate General of Health Services
Central Drugs Standard Control Organization
0/o Drugs Controller General (I)

FDA Bhawan, Kotla Road, New Delhi-110002

Date: 15 DEC 2014

ORDER

Sub: Formulae to determine the quantum of compensation in case of clinical trial related injury (other than death).

As per Rule 122DAB of Drugs and Cosmetics Rules 1945, in case of clinical trial related injury/death, the trial subject is entitled to pay financial compensation. The sponsor or his representative is required to pay the financial compensation as per the order of DCG (1). As per the Rule, the financial compensation will be over and above the expenses incurred on the medical management of the trial subject. The Appendix XII of schedule Y of the Drugs and Cosmetics Rules prescribes the procedure for processing the report of the Serious Adverse Events (SAEs) including death to arrive at the cause of the death/injury to the subject and to decide the quantum of the compensation.

The Independent Expert Committee constituted for examination of SAE of death has already devised a formula being followed for determining the quantum of compensation **in** case of clinical trial related death.

Another committee was constituted in March 2014 under the Chairmanship of Shri R. K

Jain, the then Additional Secretary & Director General (CGHS), Ministry of Health & Family Welfare, Government of India to deliberate and work out a formula to be followed to determine the quantum of compensation in case of clinical trial related injury (other than death) in accordance with the provisions of the Drugs and Cosmetics Rules. The draft formula prepared by the committee was made available for comments of public/stakeholders. After having considered the comments received, the formulae have been finalized and approved by the competent authority.

The recommendations/formulae as approved is enclosed for all concerned.

Dr G.N. Singh

Drugs Controller General (India)

To

ISCR, IDMA, OPPI, IPA and all Concerned

CC:

- **PPS to DGHS, Nirman Bhawan, Delhi.**
- **PPS to** AS & **DG (CGHS), Ministry of H&FW**
- **PS to JS(R), Ministry of H&FW**

Annexure: Recommendation

COMPENSATION FORMULAE

(CLINICAL TRIAL)

FORMULAE TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED SERIOUS ADVERSE EVENTS OF INJURY OTHER THAN DEATHS OCCURRING DURING CLINICAL TRIALS

Background

As per Rule 122DAB of Drugs and Cosmetics Rules 1945, in case of clinical trial related injury/death, the trial subject Is entitled for the financi81 compensation. The Sponsor or his representative is required to pay the compensation as per the order of DCG(1). As per the rule, the financi81 compensation will be over and *above* tile expenses incurred on the medical management of the trial subject. The Appendix XII of schedule Y of the Drugs and Cosmetic Rules prescribes the procedure for processing the reports *of* Serious Adverse ·Events (SAEs) Including death to arrive at the cause of death/Injury to the subject and to decide the quantum of compensation.

As per the procedure, in-case of Clinical Trial related SAE of death, the DCG(I) will decide the quantum of compensation after considering the recommendation of Independent Expert Committee constituted for the purpose. In case of Clinical Trial related Serious Adverse Events other than ·death, (here In referred as " Clinical Trial related SAE") the DCGI will decide the quantum of compensation considering the reports of the Investigator, Sponsor and the Ethics Committee. However, there is an option to constitute expert Committee to advise the DCG(I) In the matter.

The Independent Expert Committee constituted-for examination of SAE of deaths-has already devised a formula. being followed for determining the quantum of compensation In case of clinical trial related death which Is as under.

$$\text{Compensation} = (B \times F \times R)/99.37$$

Where,

8 =Base amount (I.e. 8-lacs)

F = Factor depending on· the age of the 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 subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

1. 0.50 terminally ill patient (expected survival not more than (NMT) *6* months)
2. 1.0 Patient with high risk (expected survival between *6* to 24 months)
3. 2.0 Patient with moderate risk
4. 3.0 Patient with mild risk
5. 4.0 Healthy Volunteers or 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.

The Apex Committee and the Technical Committee in their 7'" meeting held on 30.08.2013 and 23.08.2013 respectively, after detailed discussions agreed to the above formula for determining the quantum of compensation in cases of clinical trial related deaths. The Apex Committee in the said meeting recommended t11at a separate formula should also be worked out for determining the quantum of compensation in case of clinical trial related injury (other than death).

In view of the above, a committee was constituted under the Chairmanship of Shri R K. Jain, AS & OG comprising following members to deliberate and work out a formula to be followed to determine the quantum of compensation In case of clinical trial related Injury (other than death) in accordance with the provisions of the Drugs and Cosmetics Rules.

1. Dr. Y. K Gupta, Head, Department of Pharmacology, AIIMS, Ansari Nagar, New Delhi- 110 029
2. Dr. Arun Agarwal, Professor of ENT, Maulana Azad Medical College, Bahadur Shah Zafar Marg New. Delhi
3. Dr. B. T. l<aul, Prof. of Law, Delhi University, Law Centre – II, Dhaula Kaun, Now Delhi-110021
4. Dr Mira Shiva, Coordinator, Initiative for Heallh, Equity and Society, A-60, HauzKhas, New Delhi -110 016

The Committee in its first meeting held on 04-Apr-2014, discussed various criteria that could be considered for determination of quantum of compensation in case of Clinical Trial related SAE. The Committee opined that for calculation of quantum of compensation in such cases the guiding principle may be linked to the criteria considered for calculation of compensation in cases of death. The Committee also deliberated that 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 subject since the loss of life is the maximum injury possible.

Considering the definition of SAE, the following sequelae other than death are possible in a clinical trial subject, in which the subject shall be entitled for compensation in case the SAE is related to clinical trial.

(i) A permanent disability
(ii) Congenital anomaly or birth defect
(iii) Chronic life·lhreatening disease or
(iv) Reversible S/\E in case it is resolved. The Committee considered that unlike clinical trial related Si\E of death, the formula for determination of compensation in each of the above 4 sequelae may be different.

Accordingly, the committee in the first meeting, deliberated separately the each of t11e above four situations and worked out the draft formulae for determination of quantum of compensation in case of clinical trial related injury (other than death).

The draft formulae was uploaded on the GDSGO website for seeking the comments/suggestions of stakeholders.

In the second meeting held on **29th September 2014**, the committee deliberated separately each of the four situations in light of the comments/suggestions received on the draft formulae and decided for revisions in two situations as under:

a) In case of SAE causing permanent disability to the subject, the quantum of compensation in case of 100% disability should be 90% of the compensation which would have been due for payment Jo the nominee (s) in case of death of the subject.
The quantum for less than 100% disability will be proportional to the actual percentage disability the subject has suffered.

Accordingly, committee arrived at the following formula:

Compensation= (C x D x 90)/ (100 x 100)

Where, D= Percentage disability the subject has suffered.
C = Quantum of Compensation which would have been due for payment to the subject's nominee(s) in case of death of the subject.

b) In case of SAE causing life-threatening disease, the quantum of compensation should be linked to the number of days of hospitalization of the subject. The compensation per day of hospitalization should be equal to the wage Joss. The wage Joss per day should be calculated based upon the minimum wage of the unskilled worker (in Delhi)

Since, in case of hospitalization 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 Committee decided that the compensation per day of hospitalization In such case should be double the minimum wage. Accordingly, the committee arrived at the following formula.

Compensation = 2 x W x N

Where,

W= Minimum wage per day of the unskilled worker (in Delhi)

N= Number of days of hospitalization

In other two situations, the committee did not consider it necessary for any revision.

Recommended formula for determination of quantum of compensation In case of Clinical Trial related SAE other than death

(i) SAE causing permanent disability to the subject

In case of S/\E causing permanent disability to the subject, the Committee deliberated that so far as the quantum of compensation is concerned, 100% permanent disability to a subject rnay not be considered equivalent to the death of the subject. Therefore, even in case of 100% permanent disability, the quantum of compensation should be less than that for the death of the subject. After detailed deliberation the committee arrived at a decision that quantum of compensation in case of 100% disability should be 90% of the compensation which would have been due for payment to the nominee (s) in case of death of the subject. The quantum for less than 100% disability will be proportional to the actual percentage disability the subject has suffered,

Accordingly, the following formula is recommended.

Compensation = (CxDx90)/ (100x100)

Where,

D= Percentage disability the subject has suffered.

C= Quantum of Compensation which would have been due for payment to the subject's nominee(s) in case of death of the subject.

(ii) SAE causing congenital anomaly or birt11 defect

The committee opined that the congenital anomaly or birth defect in a baby may occur due to participation of any one 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 lumpsum amount such that if that amount is kept by way of fixed deposit or alike, It should bring a monthly interest amount which is approximately equivalent to half of minimum wage of the unskilled worker (in Delhi). This aspect was duly considered while fixing Rs. 8 lacs as base amount for determining the amount of compensation in case of SAE resulting Into death. Hence, the quantum of compensation in such cases of SAE would be half of the base amount as per formula for determini11g the compensation for SAE resulting into death.

In case of birth defect loading to (c) &(d) above to any child, the medical management as long as required would be provided by the Sponsor or his representative which will be over and above the financial compensation.

(iii) SAE causing life-threatening disease and
(iv) Reversible SAE In case it is resolved

In case of clinical trial related SAE causing life-threatening disease & reversible SAE in case it is resolved, the quantum of compensation would be linked to the number of days of hospitalization of the subject. The compensation per day of hospitalization would be equal to the wage loss. Tile wage loss per day would be calculated based upon the minimum wage of the unskilled worker (in Delhi)

Since, in case of hospitalization of my 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. The compensation per day of hospitalization in such cases would be double the minimum wage.

Accordingly, the following formula is recommended.

Compensation = 2xWxN

Where, W=Minimum wage per day of the unskilled worker (in Delhi)

N= Number of days of hospitalization.

Annexure-a

Factor (FI for calculating the amount of compensation

Age		Factors
1		2
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

Annexure 2

COMPENSATION FORMULA (CLINICAL TRIAL)

FORMULA TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED SERIOUS ADVERSE EVENTS (SAES) OF DEATHS OCCURRING DURING CLINICAL TRIALS

The Drugs and Cosmetics Rules have been amended vide GSR 53(E) dated 30-01- 2013 inserting a Rule 122DAB and a new Appendix-XII in Schedule „Y". The amendment specifies the procedure for processing of reports of Serious Adverse Events (SAEs) including deaths occurring during clinical trial to arrive at the cause of death/injury to the subject, and to determine the quantum of compensation, if any, to be paid by the Sponsor or his representative, whosoever have obtained permission from the Drugs Controller General(India) {DCG(I)} in a time bound manner.

As per the provisions of the amendment, an Independent Expert Committee shall examine the report of serious adverse event of death and give its recommendation to the Licensing Authority within 30 days of receiving the report from the concerned Ethics Committee. The DCG(I) shall, then decide the Quantum of Compensation to be paid by the Sponsor or his representative and shall pass order as deemed necessary within three months of receiving the report on the Serious Adverse Event of death.

In case of clinical trial related injury or death, the Sponsor or his representative shall pay the compensation as per the order of the DCG(I) within thirty days of the receipt of such order.

Drugs Controller General (India) constituted three Independent Expert Committees in pursuance of sub-clause (6) of appendix XII of the Schedule Y to the Drug & Cosmetics Rules 1945 on 14th March,2013 under the Chairmanship of DR. A K Agarwal, , Maulana Azad Medical College to examine the Serious Adverse Events of deaths occurring during clinical trial and to recommend the cause of death, and to determine the quantum of compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the DCG(I) .

The Committee after deliberation prepared formula to be followed for the determination of Quantum of Compensation in case of Clinical Trial related death. The details of deliberations held and the formula are as under:

1. Criteria and formula for determining the quantum of compensation in case of clinical trial related deaths

The members of Independent Expert Committee discussed the various possible factors that could be considered while deciding the quantum of compensation. The following factors emerged. (Listed below are not on the basis of priority)

F1: Age of the Subject,

F2: Risk of death,

F3: Income of the Subject,

F4: Co- morbidity of the subject at the time of SAE (Death),

F5: Expected Survival,

F6: Dependency on the deceased

F7: Concomitant medication ,

F8: Gender of the subject

F9: Negligence during the conduct of Clinical Trial

F10: Duration of the disease

F11: Industry V/s Academia V/s Institute v/s Sponsor,

F12: Expectedness of drug to cause death.

After deliberation in detail the committee agreed that although in ideal situation factors from F1 to F12 should be considered in deciding the quantum of compensation, however the committee felt that ,in order to have a formula which is simple yet meeting all important points be considered and the less important factors which will largely increase the complexity, be excluded. Thus a best fit formula need to be adopted.

The following criteria were finally adopted.

1. The criteria should not be discriminative in nature due to socio-econimic conditions e.g. (a) income, (b) education

2. The criteria should not discriminate gender/sex

3. The criteria should not be such which may have minimal impact but may create large variability.

4. The formula should be such that the inter group variability of compensation value so arrived at, has little scope of discretion, thus avoid possible bias.

Thus, the following criteria were finally decided to be incorporated in the compensation formula.

i) Age of the subject
ii) Risk factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial.

a) Consideration of the age of the subjects

The committee noted that The Workmen Compensation Act prescribes the factors (based on age) for calculation of the lump sum amount of compensation to be paid by the employer in case of permanent disablement and death depending upon age of the injured. The factor ranges from 99.37 (for age of 65 or more) to 228.54 (of age not more than 16) depending upon the age of the injured. The table of the Workmen Compensation Act is at **Annexure A**. After deliberating the above, it was suggested that the same factor may be applied for considering the age of the subject while calculating the amount of compensation in case of clinical trial related death.

The rationale for taking the age factor as per the Workmen Compensation Act is that both are in general "No Fault Compensation" and the committee felt that both the situations are comparable so far as age factor is concerned.

b) Risk Factor:

After detailed discussion it was decided that the risk factor shall be divided in a scale of 0.50, 1.0, 2.0, 3.0 and 4.0. However in case of patients whose expected mortality is 90 % or more within 30 days, a fixed amount of Rs. 2 lac may be given. The five grade of the scale is divided as follows:-

1. 0.50 terminally ill patient (expected survival not more than (NMT) 6 months)
2. 1.0 Patient with high risk (expected survival between 6 to 24 months)
3. 2.0 Patient with moderate risk
4. 3.0 Patient with mild risk
5. 4.0 Healthy Volunteers or subject of no risk

c) Need and criteria to have a base amount

The Committee deliberated and agreed that a constant base factor (amount) based on logic should be there, on which the variables (age & risk) should be applied upon to determine the quantum of compensation on case to case basis.

Several rounds of discussion were held to decide a base amount. A figure of 4 lacs was considered based on Railway Accident and Untoward Incidence (Compensation) Rules,

1990. A figure of 6 lacs was also deliberated on the logic of making the nominee of the deceased a reasonable amount available. However, the committee finally decided to a base amount that is more logical and which remains contemporary / dynamic.

After detailed deliberation the committee decided that base amount should be such that if the nominee of the subject keeps that amount of compensation in bank by way of fixed deposit, he or she will get an monthly interest amount which is at least approximately equivalent to the minimum wages (reference: Minimum wages of Delhi) of the unskilled workers.

It was deliberated that the minimum wages as on date is Rs. 7722.00 per month and accordingly a base amount (rounded) of Rs. 8.0 Lakhs would be appropriate. It was also decided that this base amount should refer to the age of 65 yrs which corresponds to the factor of 99.37 of the table of Worksmen Compensation Act. It is evident that the base amount will increase /change with the revision of minimum wage.

Computing the 3 factors viz. a) Age b) Risk and c) base amount, following formula emerged for deciding the quantum of compensation in case of SAE (Death) related to clinical trial:

Compensation = (B X F X R)/99.37

Where, B = Base amount (i.e. 8 lacs) F = Factor depending on the age of the 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 subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

1 .0.50 terminally ill patient (expected survival not more than (NMT) 6 months)
2. 1.0 Patient with high risk (expected survival between 6 to 24 months)
3. 2.0 Patient with moderate risk
4. 3.0 Patient with mild risk
5 4.0 Healthy Volunteers or 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.

Thus, it will be seen that the compensation amount will vary from a minimum of Rs.4 lacs to a maximum of Rs.73.60 lacs depending on the age of the deceased and the risk factor. However, in case of patients whose expected mortality is 90 % or more within 30 days, a fixed amount of Rs. 2 lac should be given.

The committee will examine cases of SAEs of deaths and decide the final quantum of compensation after due diligence and application of mind on the risk factor and recommend the same to DCG(I) on case to case basis. The committee also considered the above formula as provisionally final.

Annexure A:

Factor (F) for calculating the amount of compensation.

	Age	**factors**
	1	2
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	221.79
	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

Annexure 3

List of Notified Medical Devices

The following medical devices are notified under the Drugs and Cosmetics Act:

- Disposable Hypodermic Syringes
- Disposable Hypodermic Needles
- Disposable Perfusion Sets
- In vitro Diagnostic Devices for HIV, HbsAg and HCV
- Cardiac Stents
- Drug Eluting Stents
- Catheters
- Intra Ocular Lenses
- I.V. Cannulae
- Bone Cements
- Heart Valves
- Scalp Vein Set
- Orthopedic Implants
- Internal Prosthetic Replacements

Registration is not required for import of non-notified medical devices in India. However, the few devices are regulated as "Drugs" under Drugs and Cosmetics Act and Rules, hence registration and import license is required for import in to India:

- Blood Grouping Sera
- Ligatures
- Sutures
- Staples
- Intra Uterine Devices (Cu-T)
- Condoms
- Tubal Rings
- Surgical Dressing
- Umbilical Tapes
- Blood / Blood Component Bags

In Vitro Diagnostic Categories	
Class A	(1)if it is a reagent or an article which possesses any specific characteristic that is intended by its product owner to make it suitable for an in vitro diagnostic procedure related to a specific examination;

	(2)an instrument intended specifically to be used for an in vitro diagnostic procedure; or (3)a specimen receptacle
Class B	**IVD for:** (1)test results that are not for the determination of a medically critical status; or (2) preliminary test results which require confirmation by appropriate laboratory tests
Class C	An in vitro diagnostic medical device shall be assigned to Class C, if it is to be used for near-patient testing in a blood gas analysis or a blood glucose determination. Illustration: Anticoagulant monitoring, diabetes management, and testing for C- reactive protein and Helicobacter pylori.
	In vitro diagnostic medical device shall be assigned to Class C, if it is intended to be used for self-testing.
	intended to be used for blood grouping or tissue typing to ensure the immunological compatibility of any blood, blood component, blood derivative, cell, tissue or organ that is intended for transfusion or transplantation, as the case m
	IVD for • detecting the presence of, or exposure to, a sexually transmitted agent • detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation (for example, Cryptococcus neoformansor Neisseria meningitidis); • detecting the presence of an infectious agent, where there is a significant risk that an erroneous result will cause death or severe disability to the individual or foetus being tested (for example, a diagnostic assay for Chlamydia pneumoniae, Cytomegalovirus or Methicillin-resistant Staphylococcus aureus); • pre-natal screening of women in order to determine their immune status towards transmissible agents such as immune status tests for Rubella or Toxoplasmosis • determining infective disease status or immune status, where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient being tested (for example, Cytomegalovirus, Enterovirus or Herpes simplex virus in transplant patients) • screening for disease staging, for the selection of patients for selective therapy and management, or in the diagnosis of cancer; • human genetic testing, such as the testing for cystic fibrosis or Huntington's disease; • monitoring levels of medicinal products, substances or biological components, where there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient being tested (for example, cardiac markers, cyclosporin or prothrombin time testing); • management of patients suffering from a life-threatening infectious disease such as viral load of Human immunodeficiency virus or Hepatitis C virus, or genotyping and sub-typing Hepatitis C virus or Human immunodeficiency virus) • screening for congenital disorders in the foetus such as Down syndrome or spina bifida

Class D	intended to be used for blood grouping or tissue typing according to the ABO system, the, the Duffy system, the Kell system, the Kidd system, the rhesus system (for example, HLA, Anti-Duffy, Anti-Kidd)
	intended to be used for detecting the presence of, or exposure to, a transmissible agent that,- (1) is in any blood, blood component, blood derivative, cell, tissue or organ, in order to assess the suitability of the blood, blood component, blood derivative, cell, tissue or organ, as the case may be, for transfusion or transplantation; or (2) causes a life-threatening disease with a high risk of propagation.

Annexure 4

List of Non Notified Medical Devices

The following medical devices are non notified under the Drugs and Cosmetics Act:

Medical Devices	
Class A	Non-invasive medical devices which come into contact with injured skin, if it is intended to be used as a mechanical barrier, for wounds which have not breached the dermis and can heal by primary intention.
	Non-invasive medical devices for channelling or storing body liquids or tissues or liquids or gases for the purpose of eventual infusion, administration or introduction into a human body
	Non- invasive medical device if it, does not come into contact with a person or comes into contact with intact skin only.
	Invasive (body orifice) medical devices for transient use (except for use on the external surface of any eyeball or liable to be absorbed by the mucous membrane)
	Invasive (body orifice) medical devices for short term use for use in an oral cavity as far as the pharynx or in an ear canal up to the ear drum or in a nasal cavity; or not liable to be absorbed by the mucous membrane
	Surgically invasive medical devices for transient use if it's a reusable surgical instrument
	Active diagnostic medical devices intended to be used solely to illuminate a patient's body with light in the visible or near infrared spectrum
	Medical devices incorporating animal or human cells, tissues or derivatives if it incorporates non-viable animal tissues, or their derivatives
Class B	Non-invasive medical devices which come into contact with injured skin, if it is intended to be used principally with wounds which have breached the dermis, or is principally intended for the management of the microenvironment of a wound

	Non-invasive medical devices for channeling or storing substance if it is intended to be connected to an active medical device which is in Class B, C or D
	Non-invasive medical devices for modifying compositions carried out by filtration, centrifuging or any exchange of gas or of heat.
	Invasive (body orifice) medical devices for transient use for use on the external surface of any eyeball or liable to be absorbed by the mucous membrane
	Invasive (body orifice) medical devices for short term use (except is intended for use in an oral cavity as far as the pharynx or in an ear canal up to the ear drum or in a nasal cavity; and or not liable to be absorbed by the mucous membrane)
	Invasive (body orifice) medical devices for long term use intended for use in an oral cavity as far as the pharynx or in an ear canal up to the ear drum or in a nasal cavity; or not liable to be absorbed by the mucous membrane
	Invasive (body orifice) medical devices for connection to active medical devices
	Surgically invasive medical devices for transient use (except it's a reusable surgical instrument, intended for the supply of energy in the form of ionizing radiation, intended to have a biological effect or to be wholly or mainly absorbed by the human body, intended for the administration of any medicinal product by means of a delivery system and such administration is done in a manner that is potentially hazardous, intended to be used specifically in direct contact with the central nervous system or for the diagnosis, monitoring or correction of a defect of the heart or of the central circulatory system through direct contact with these parts of the body)
	Surgically invasive medical devices for short term use (except intended to undergo a chemical change in the body, intended for the administration of any medicinal product or the supply of energy in the form of ionising radiation, intended to have a biological effect or to be wholly or mainly absorbed by the human body or to be used specifically in direct contact with the central nervous system or for the diagnosis, monitoring or correction of a defect of the heart or of the central circulatory system through direct contact with these parts of the body)
	Implantable medical devices and surgically invasive medical devices for long term use if placed into any tooth
	Active therapeutic medical devices for administering or exchanging energy (except administration or exchange of energy may be done in a potentially hazardous way or to be used to directly influence the performance, of a Class C active therapeutic device)
	Active diagnostic medical devices
	Medical devices incorporating medicinal products exempted from the licensing requirements

	Medical devices for sterilization or disinfection if it is intended for the disinfection of any other medical device before the latter is sterilized or undergoes end-point disinfection
Class C	Non-invasive medical devices which come into contact with injured skin, if it is intended to be used principally with wounds which have breached the dermis and cannot heal by primary intention

	Blood bag that does not incorporate a medicinal product
	Non-invasive medical devices for modifying compositions of the biological or chemical composition of blood or other body liquids or other liquids intended for infusion into the body.
	Invasive (body orifice) medical devices for long term use (except is intended for use in an oral cavity as far as the pharynx or in an ear canal up to the ear drum or in a nasal cavity; and or not liable to be absorbed by the mucous membrane)
	Surgically invasive medical devices for transient use if intended for the supply of energy in the form of ionizing radiation ; intended to have a biological effect or to be wholly or mainly absorbed by the human body; intended for the administration of any medicinal product by means of a delivery system and such administration is done in a manner that is potentially hazardous
	Surgically invasive medical devices for short term use intended to undergo a chemical change in the body, intended for the administration of any medicinal product or the supply of energy in the form of ionizing radiation
	Implantable medical devices and surgically invasive medical devices for long term use (except placed into any tooth, to be used in direct contact with the heart, the central circulatory system or the central nervous system; to be life supporting or life sustaining, to be an active medical device, to be wholly or mainly absorbed by the human body, for the administration of any medicinal product; breast implant or intended to undergo chemical change in the body)
	Active therapeutic medical devices for administering or exchanging energy administrated or exchange of energy may be done in a potentially hazardous way or to be used to directly influence the performance, of a Class C active therapeutic device

	An active diagnostic medical device • if it is intended by its product owner specifically for: ❖ the monitoring of vital physiological parameters, where the nature of any variation is such that it could result in immediate danger to the patient (such as any variation in cardiac performance, respiration or activity of the central nervous system); or ❖ Diagnosing in a clinical situation where the patient is in immediate danger. • Intended for the emission of ionising radiation and to be used in diagnostic or interventional radiology. • intended for the control or monitoring, or to be used to directly influence the performance, of any active diagnostic medical • an active medical device if the administration or removal of the medicinal product, body liquid or other substance is done in a manner that is potentially hazardous, taking into account: o the nature of the medicinal product, body liquid or substance; ❖ the part of the body concerned; and ❖ the mode and route of the administration or removal.
	Medical devices for sterilization or disinfection (except if it is intended for the disinfection of any other medical device before the latter is sterilized or undergoes end-point disinfection)
	Medical devices for contraceptive use(except if it is implantable)
Class D	Surgically invasive medical devices for transient use if intended to be used specifically in direct contact with the central nervous system or for the diagnosis, monitoring or correction of a defect of the heart or of the central circulatory system through direct contact with these parts of the body)

	Surgically invasive medical devices for short term use intended to have a biological effect or to be wholly or mainly absorbed by the human body or to be used specifically in direct contact with the central nervous system or for the diagnosis, monitoring or correction of a defect of the heart or of the central circulatory system through direct contact with these parts of the body)
	Implantable medical devices and surgically invasive medical devices for long term use to be used in direct contact with the heart, the central circulatory system or the central nervous system; to be life supporting or life sustaining, to be an active medical device, to be wholly or mainly absorbed by the human body, for the administration of any medicinal product; breast implant or intended to undergo chemical change in the body
	Medical devices incorporating medicinal products (Except if medical product is exempted from the licensing requirements)
	Medical devices incorporating animal or human cells, tissues or derivatives (except it incorporates non-viable animal tissues, or their derivatives)
	Medical devices for contraceptive use if it is implantable