Clinical Research Regulations

India

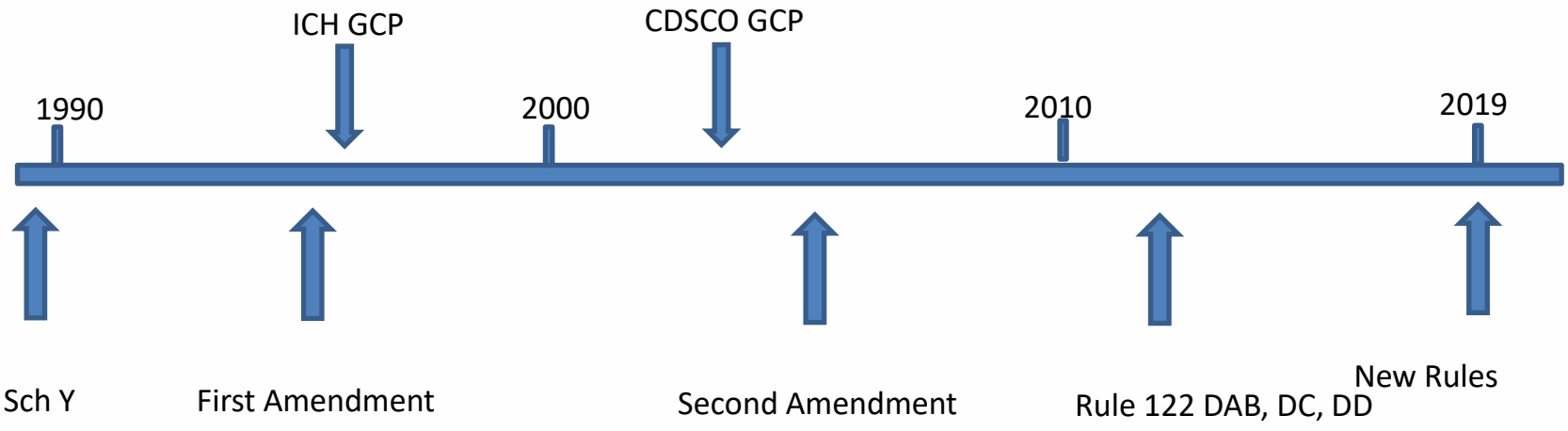
Module 5 Topic 1

Regulations and Guidelines

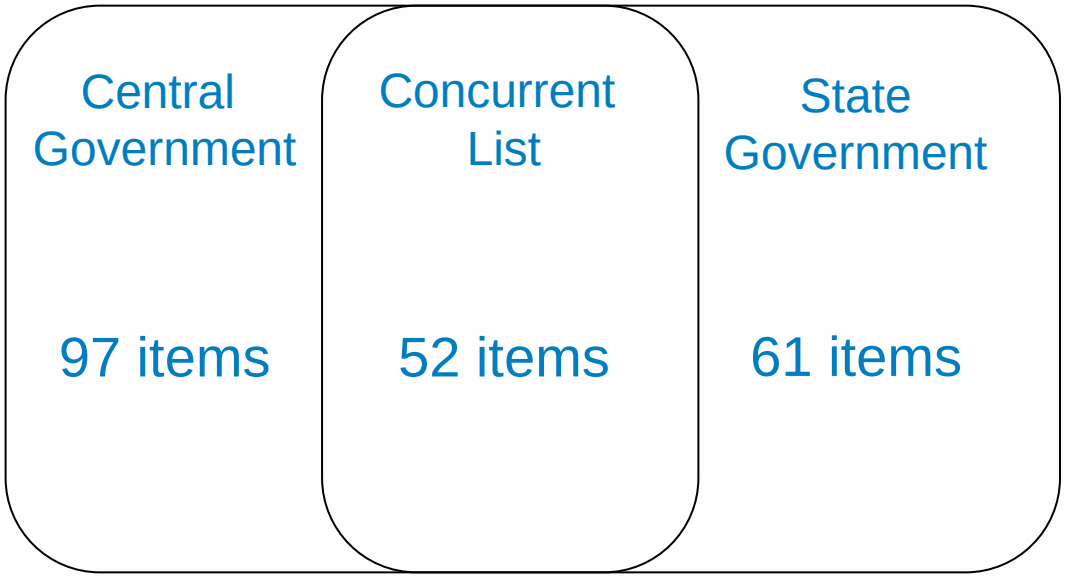
A **regulation** is a rule or directive made and maintained by an authority, in India it is a competent authority. The final body to make rules is the Parliament, it can give another body the power to make a rule on its behalf. Regulations are legally binding.

A **guideline** is information intended to advise as to how a particular activity should be completed. It is recommendatory and not mandatory, in that one cannot be punished for violating a guideline.

The Regulation Timeline



Federal Structure



Implementing Authorities

Central Government:

- Central Drugs Standard Control Organization(CDSCO)

Drugs Controller General (India)

State Governments:

- State Drug Controller

In some states known as

- Commissioner, FDA

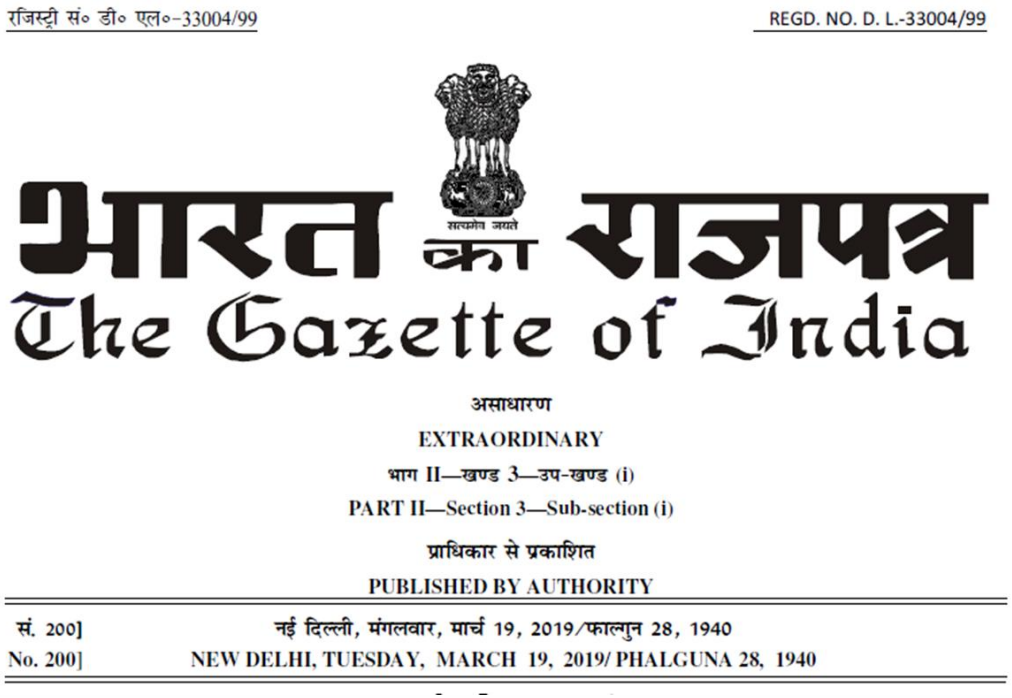
Central and State Authority

Central Government	State Government
Import Export New Drugs	Manufacture Distribution Sale

Act and Rules

- Act lays down the principle
- Drugs and Cosmetics Act (1940) runs in 35 pages
- Rules provide the procedure to follow the Act.
- Drugs and Cosmetics Rules (1945) run in 518 pages

New drugs and Clinical Trial Rules 2019



रजिस्ट्री सं० डी० एल०-33004/99 REGD. NO. D. L.-33004/99

भारत का राजपत्र

The Gazette of India

असाधारण

EXTRAORDINARY

भाग II—खण्ड 3—उप-खण्ड (i)

PART II—Section 3—Sub-section (i)

प्राधिकार से प्रकाशित

PUBLISHED BY AUTHORITY

सं. 200] नई दिल्ली, मंगलवार, मार्च 19, 2019/फाल्गुन 28, 1940

No. 200] NEW DELHI, TUESDAY, MARCH 19, 2019/ PHALGUNA 28, 1940

The Government of India has published the New Drugs and Clinical Trials Rules 2019 have been published on 19 March 2019. These will supersede **Part XA** and **Schedule Y** of the Drugs and Cosmetics Rules 1945. For Medical Devices **Part XA** and **Schedule Y** continue

What's Good? Arrangement

All definitions under one section

2. Definitions

(1) In these rules, unless the context otherwise requires,

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

New Rules Chapters

Chapter	Subject
I	Definitions
II	Authorities
III	Ethics Committee for CT or BA/BE
IV	Ethics Committee for Health Research
V	Conduct of CT & BA/BE
VI	Compensation
VII	BA/BE Centre
VIII	Manufacture of new drugs for CT & BA/BE
IX	Import of new drug for CT/BA/BE
X	Import or Manufacture for Sales & Marketing
XI	Import or Manufacture for use in govt hospitals
XII	Miscellaneous

Schedules

Schedule	Topic
Schedule - 1	General Principles for CT
Schedule - 2	Requirements for Import & Manufacture
Schedule - 3	Conduct of CT
Schedule - 4	Conduct of BA/BE
Schedule - 5	Post Marketing Studies
Schedule - 6	Fees payable
Schedule - 7	Compensation formula

Definitions

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

If a word or a term is used in both documents (D&C Act and the NDCTR 2019), the meaning as given in NDCTR 2019 shall prevail.

Clinical Trial

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

(i) clinical or;

(ii) pharmacological including pharmacodynamics, pharmacokinetics or;

(iii) adverse effects,

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

Academic Clinical Trial

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

An academic clinical is not a Biomedical and Health Research Study.

Biomedical and Health Research

Includes studies on basic , applied and operational research or clinical research designed primarily to increase knowledge about diseases or conditions (physical or socio-behavioural) their detection and cause; and evolving strategies for health promotion, prevention or amelioration of disease and rehabilitation but does not include clinical trials as defined in these rules.

Ethics Committee

"Ethics Committee" means, for the purpose of, -

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

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

New Drug

- “new drug” means,—

  (i) a drug, which has not been used in the country to any significant extent, has not been approved by CLA

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

  (iii) a fixed dose combination of two or more drugs, (New for 4 years)

  (iv) a modified or sustained release form of a drug or novel drug delivery system

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

Miscellaneous

- “orphan drug” means a drug intended to treat a condition which affects not more than five lakh persons in India;

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

Post Trial Access

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

Similar Biologic (Biosimilar)

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

Chapter V-Regulatory Approval

19 (1) No person or institution or organization shall conduct clinical trial of a new drug or investigational new drug,

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

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

Regulatory Approval

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

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

Regulatory Approval

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

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

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

22. Grant of trial permission

(1) The CLA may, after scrutiny of documents furnished with the application in Form CT-04,—

(i) grant the permission to conduct clinical trial in Form CT-06;

(ii) in case of deficiencies in the application inform the applicant about the deficiencies;

(iii) if not satisfied reject the application, with reasons recorded in writing.

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

Clinical Trial Permission

Permission for drugs of Indian origin in 30 days. At the end of 30 days if no reply from DCGI, assumed permission.

Permission for drug approved abroad in 90 days, automatic permission cannot be presumed

Other Conditions

25.i The trial can be initiated after permission of the Registered EC of the site.

25.ii If the site does not have a registered EC, then permission of another EC within 50 km distance may be sought.

25.iv CLA shall be informed of the ethics approval within 15 days of approval.

25.v Clinical trial shall be registered with the Clinical Trial Registry of India.

Other Conditions

25. vi Trial shall be conducted in accordance with the approved clinical trial protocol and other related documents and as per GCP and NDCTR.

25.vii Status of enrolment of subjects shall be submitted to the CLA on quarterly basis.

25.viii Six monthly status report of the trial submitted through Sugam.

25.ix Detailed reasons for termination shall be communicated to the CLA within 30 days

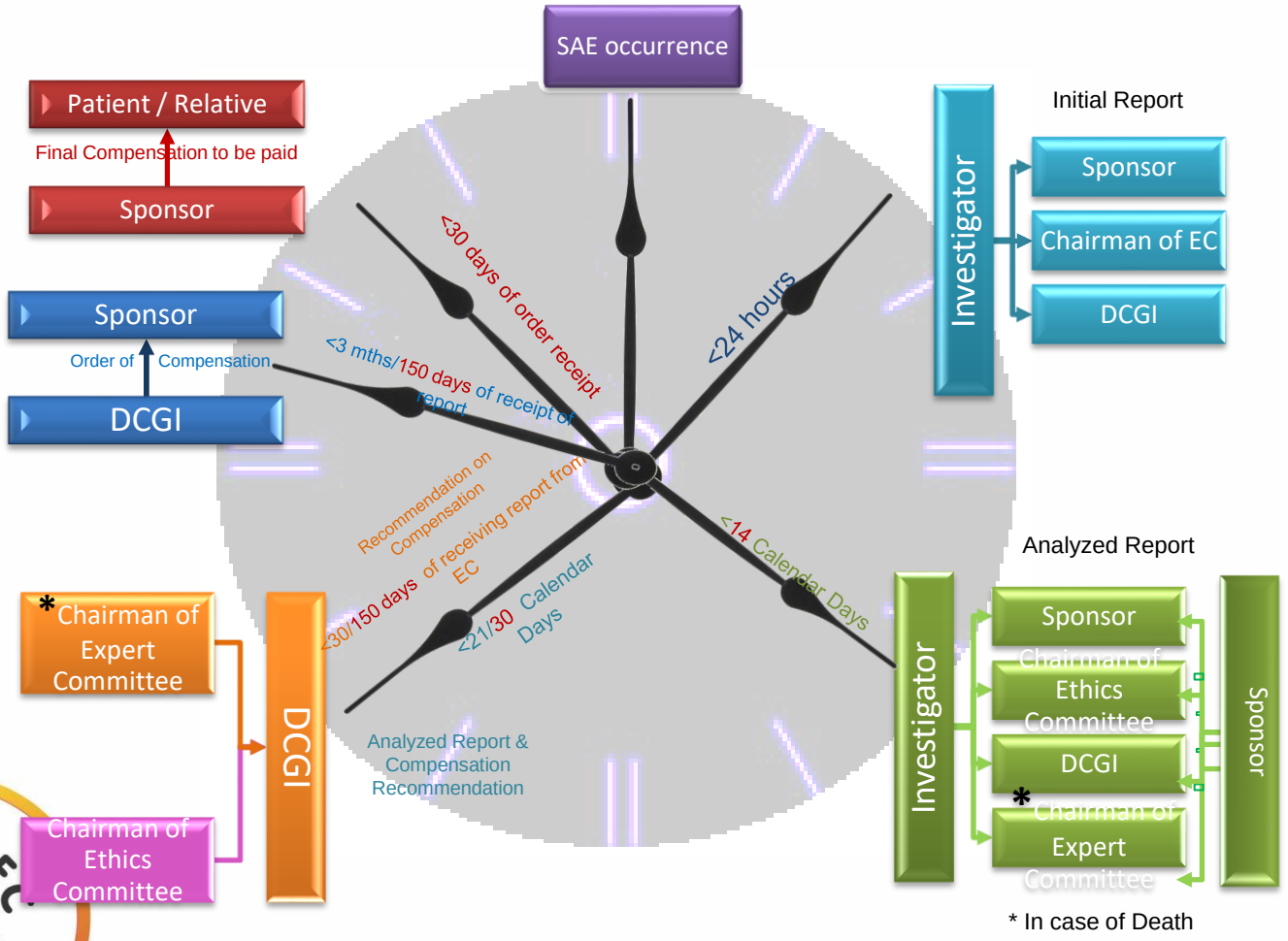
SAEs

25. xii In case of injury or death, reimbursement of medical/surgical expenses and compensation to be paid.

25.xiii The sponsor and the site is liable to be inspected by officers of CLA.

25.xiv If the new drug is found to be useful, the sponsor shall apply to the CLA for permission to import or manufacture the drug for sale as per Chapter X.

New SAE Reporting Process



Compensation Chapter VI

39. Compensation in case of injury or death in clinical trial or bioavailability or bioequivalence study of new drug or investigational new drug.

40. Medical Management in clinical trial or bioavailability and bioequivalence study of new drug or investigational new drug

41. Consideration of injury or death or permanent disability to be related to clinical trial or bioavailability and bioequivalence study.

42. Procedure for compensation in case of injury or death during clinical trial, bioavailability and bioequivalence study

Compensation

39. In case of death or permanent injury to a subject, financial compensation shall be provided as per rule 42. The compensation shall be in addition to any expenses incurred on medical management of the trial subject. In the event of a non permanent injury, the quantum of compensation shall be commensurate with the loss of wages. The sponsor shall give an undertaking with the application for trial permission to provide compensation in the case of trial related injury or death.

Compensation to?

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

(2) Third Schedule Table 3

Name and address of the **nominees** and his relation to the subject (for the purpose of compensation in case of trial related death).

Compensation

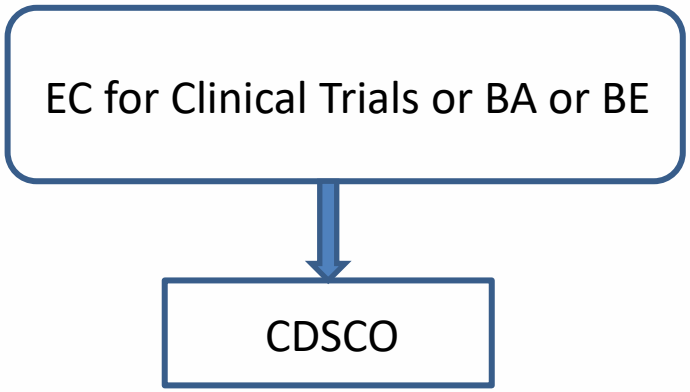
- The compensation required to be paid for trial related injuries is identical for Clinical Trials, Bioavailability, Bioequivalence Study, Biomedical and Health Research.
- It is unimportant whether the study is observational/investigator driven, compensation rule is the same.
- The risk of SAEs in observational and investigator driven studies is low
- The resources available for observational and investigator driven studies are low, hence payment of compensation may be difficult.

PMS

- Both Phase IV and PSUR are required.
- Regulatory permission for Phase IV studies, using approved protocol under Fifth Schedule

- PSUR
  - every six months for the first two years
  - Annually for two years

Ethics Committees



Deferred for 180 days

Composition (EC for CT, BA/BE)

The Ethics Committee shall have a minimum of seven members from medical, non medical, scientific and non scientific areas, with at least

- One lay person
- One woman member
- One legal expert
- One independent member from any other related field such social scientist or representative of a non government voluntary agency or philosopher or ethicist or theologian.

(Quorum requirement state the need for basic medical scientist)

Composition (CT for B & HR)

The Ethics Committee for Biomedical and Health Research shall have the composition as described by ICMR guidelines (2017)

- Clinicians
- Basic Medical Scientists
- Legal Expert
- Lay person
- Social worker or NGO member, philosopher etc.

Conditions

- At least 50% members should be non affiliated.
- Each member should undergo training as specified by CLA (as yet no syllabus or agency has been specified for training), untrained members shall be disqualified from becoming a member.
- Medical scientists and clinicians must hold a post graduate degree.
- Experts may be called in when studies are on special patient groups or in areas where the EC feels the need.

Tenure of members

- The NDCTR 2019, does not specify the tenure for which a member may continue to be a member of the Ethics Committee.
- NABH 1.33 states “Membership, appointment, reconstitution and resignation shall be decided as per terms of reference.”
- ICMR Guideline 4.3.3. states “Generally the term of EC membership may be 2 to 3 years. The duration could be extended as per the SOPs. A defined percentage of members could be changed on a regular basis.”

Responsibilities of the EC

11.(i) review and accord approval to a clinical trial, bioavailability or bioequivalence study protocol and other related documents, in the specified format in and oversee the conduct of clinical trial to safeguard the rights, safety and wellbeing of trial subjects in accordance with these rules, Good Clinical Practices Guidelines and other applicable regulations;

Responsibilities of the EC

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

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

Responsibilities of the EC

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

Responsibilities of the EC

11 (v) where it comes to a conclusion that the trial is likely to compromise the right, safety or wellbeing of the trial subject, the committee may order discontinuation or suspension of the clinical trial under intimation to the head of the institution and CLA;

11(vi) allow officers of CLA to enter, inspect any record, or documents, and answer any query raised by them to verify compliance with GCP Guidelines for safeguarding the rights, safety and well-being of trial subjects;

Timelines

S.No	Activity	Timeline
1	Registration of an EC	45 days
1.1	Appeal in case of refusal	60 days
1.2	Decision on appeal	60 days
1.4	Re registration	45 days
2	Permission to conduct Clinical Trial (drug developed in India)	30 days*
3	Permission to conduct Clinical Trial (drug approved outside)	90 days
4	Permission to conduct BA/BE Study	90 days

Fees Payable

Rule	Subject	Amount
21	Conduct Trial Phase I	Rs. 3,00,000
21	Conduct Trial Phase II	Rs. 2,00,000
21	Conduct Trial Phase III	Rs. 2,00,000
21	Conduct Trial Phase IV	Rs. 2,00,000
33	Conduct BA/BE Study	Rs. 2,00,000
59	Manufacture New Drug for Test	Rs. 5,000
67	Import New Drug for Test	Rs. 5,000
75	Import New Drug for Sale	Rs. 5,00,000
75	Import Finished Product for Sale	Rs. 5,00,000

Post Trial Access

Where an investigator of investigational new drug or new drug has recommended post-trial access of the drug to any trial subject and has been approved by the Ethics Committee, the post-trial access shall be provided by the sponsor free of cost,—

(i) if the trial is for an indication with no alternative and

(ii) the trial subject or legal heir, has consented to use post-trial drug; and the investigator has certified no liability for sponsor in post- trial use of drug.

Rule 27

- Post trial access is now a part of the rule, not at the mercy of the sponsor.
- if no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and
- the trial subject or legal heir has consented in writing to use post-trial investigational new drug; and has declared in writing that the sponsor shall have no liability

Chapter XII

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

NABH Accreditation

Is it mandatory?

F.No. 12-01/14-DC Pt.47/DRS. Dated 28th Nov 2016

This was correspondence between the Government of India and CDSCO and does not mean that it was an order for ECS

NDRS 2019 makes no mention of NABH, it replaces Part XA of D&C Rules and Schedule Y, which don't speak of NABH either.

EC Proficiency

Registration Status	Institutional	Independent	Total
Initial Registration	881	220	1101
Eligible for Re registration	641	176	817
Re registered	386	48	434
NABH Applied	180	0	180
NABH Accredited	109	2	111

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