WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 7, 272-298. Review Article ISSN 2277– 7105

A BRIEF REVIEW OF AMENDMENTS SCHEDULE Y (2005-2018) AND NDCT RULES 2019

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Article Received on
24 April 2020,

Revised on 15 May 2020,
Accepted on 05 May 2020,

DOI: 10.20959/wjpr20207-17642

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ABSTRACT

India considered as a hub for conducting clinical trials, the Central Drugs Standard Control Organization (CDSCO), headed by Drug Controller General of India (DCGI), lays down the regulations for the conduct of clinical trial in India. The importance of clinical trials in promoting health services cannot be overemphasized. Because of conducting clinical trial on a new molecule/entity improve the quality and lifespan of patients in compliance with safety. While it is important that the number of clinical trials increases, the Government is also trying to ensure the right, safety and well-being of participants in clinical trial, and also ensure the quality of trial performed in India improve their standard in compliance with regulations, thus for further review on the changes in regulatory aspects introduced subsequently and their impact on clinical trial. Some proposals of amendment in D&G rules have been approved by Drug Technical Advisory Board (DTAB). The Government introduced the New Drugs and Clinical Trial Rules on 19th Mar 2019, to replace Part XA and Schedule Y of the Drugs and Cosmetics Rules 1945, and it applied on 25th Mar 2019. Many changes have been made in the NDCT rules to help Clinical research, clinical trial and BA/BE study in India like timelines for many regulatory functions, duplication of rule numbers is likely to complicate the regulatory procedures, Classification of Ethics committee, compensation and remove some discrepancies. The Government would do well to consider the suggestions made herein and amend the New Drugs and Clinical Trial Rules 2019. This article summarizes the essential changes information, impact, and brief description of NDCT rules 2019.

KEYWORDS: Drug and Cosmetics act, New Drugs and Clinical Trial rules 2019, Schedule Y, Ethics Committee, Central Drugs Standard Control Organization (CDSCO), Drug Controller General of India (DCGI), Ministry of Health and Family Welfare (MoHFW).

INTRODUCTION

The Drug and Cosmetics act (1940) and the Drug and Cosmetics rules (D&C) (1945) are the main regulatory operating law in India. It complies for the sale of drugs, distribution, and Manufacture, cosmetic & medical devices and to ensure safety, efficacy and quality, of conducting clinical trials. It binds with allopathic and other system of medicine for regulate import under the D&C act 1940 and D&C rules 1945 in India, it has been amended from time to time. The guidelines and requirements for clinical trial are specified in schedule Y. The initiation of clinical trial is essential for generating data in compliance with essential documents (approved protocol, etc), and also in compliance with the provision of Drug & Cosmetics rule 1945, the right, safety, well-being and confidentiality of the participants is the major concern for the initiation of clinical trial. As the regulatory world is dynamic and the amendments (changes) are very essential for smoothly conducting or initiating the clinical trial, as now a days the rate of issues related with clinical trial increases so it's a major area of concern, these changes should be made with the existing law to addressing or resolved the evolving issues. Since 2016 to last update of 19th Mar 2019 the Indian regulatory authorities have announced a spate of laws and guidelines, which will have a huge impact on the clinical trial sector in India.

History

The evolution journey of clinical research has a long and fascinating. History of clinical research and trails across the world covers a wide variety of challenges like scientific, ethical and regulatory. The ethical principles for human safety, it has been including several turning points - Nuremberg Code, Declaration of Helsinki, Belmont Report 1996, and International Conference on Harmonization-Good Clinical Practice guidance. Similarly, to ethical guidelines, clinical trials started to become embodied in regulation as government authorities began recognizing an importance for controlling medical research & therapies in the early 20th century. As the scientific progress continues to happen, there will be new ethical and regulatory challenges requiring dynamic updates in ethical and legal pattern of clinical trials.

Evolution of Clinical Trials in India

In early decade of 20th century, many conscienceless foreign companies over flow the Indian research and manufacture market with spurious and adulterated drugs. The government formed a Chopra committee i.e. drug inquiry committee under the Sir Ram Nath Chopra after that "The Drug Bill" amended to the Drug and Cosmetic Act 1940 (D and C Act) and Drug and Cosmetic Rules of 1945.[3] This is the central statute that regulates India's drug and cosmetic import, manufacture, distribution and sale, and also established the Central Drugs Standard Control Organization (CDSCO), under the Drugs Controller General (India) (DCG(I)).[4] The CDSCO is a division in Ministry of Health and Family welfare, Government of India, Directorate General of Health services, headed by Drug Controller General of India (DCGI). The CDSCO has four zonal, three sub-zonal and seven port/airport offices and six laboratories to carry out its activities.[5]

Traditional Medicine of Ayurveda has a rich heritage in India. However, there is no any ethical documentation recorded in the history of any clinical experiments. That time India has been recognized as an attractive country for clinical research. The first meeting for research was held on November 15, 1911 at the Plague Laboratory, Bombay, under the Chairmanship of Sir Harcourt Butler by the Indian Research Fund Association (IFRA), But the historical decision was taken to start a journal for Indian medical research in the 2nd meeting of the governing body in 1912.[1]

The Indian government, realizing the potential of clinical research for new therapies, has modified and amended Schedule Y to the Drug and Cosmetics Rules of 1945. The first research unit of IRFA in the India was established at the Indian Cancer Research Centre, Bombay in 1945. Indian Research Fund Association has been changes to Indian Council of Medical Research in 1949.

The set of guidelines and requirements for clinical trials established under schedule Y. After the introduction of strict patent rules in the area of clinical research led the government to introduce many changes, as Schedule Y was written with the generics industry mind set but it modify as increase entry of foreign pharmaceutical companies. The Ethical and Regulatory guidelines developed by the government after recognized their importance in regulation. The Ethical Guidelines for Biomedical Research on Human participants issued by the Indian council of Medical Research (ICMR) in 2000 and Indian Good Clinical Practice (GCP) guidelines released by CDSCO in 2001.

Amendments in schedule Y (2005–2011)

The regulatory guidelines for clinical research established under schedule Y of drug and cosmetic Act in1988 and revision of schedule Y in Jan 2005.[2] The revised schedule Y 2005 provided Pragmatic definition of Clinical trial phase I to IV, which eliminated the Phase lag.[6] This schedule specified Good Clinical Practice, responsibilities of ethics committee (EC), Principle investigator (PI) and sponsor and explained formats for critical and essential documents likes Study related Protocol, Informed consent documents, clinical study report, EC approval documents, reporting of adverse event and serious adverse event, Requirements for notifying changes in protocol and then, application of Product patent. Schedule Y(2005) given a direction of GCP compliance trials and have provided the much-needed regulatory support to GCP guidelines. Clinical trials have evolved into a standardized procedure, focusing on scientific assessment of efficacy and guarding the patient safety. In 2007, the government took another step for clinical research to drug-development industry removed the 12% service tax on clinical trials.[7] Previously, an export license was required to get samples out of India but it has been removed to save the time, In February 2009. In order to further build up the scientific review and approval of new drugs/devices, the ministry of health and family welfare has selected 12 New Drug Advisory Committee's (NDAC) and 7 Medical Device Advisory Committee's (MDAC) to suggest the CDSCO in making their decisions on approval of new drugs and global clinical trials, the NDAC expert committees have started reviewing the global clinical trial documents, from 2011.

The ministry of health and family welfare (MoHFW) has took strong step to protect the rights of the subjects participating in clinical trials (CTs), by the notifying three amendments to drugs and cosmetic rules namely Rule 122 DAB (1st amendment)[9], Rule 122 DAC (2nd amendment)[9] and Rule 122 DD (3rd rule).[9] The device/pharma/biotech industry/contract research organization (CROs)/academic investigators and regulators themselves faced challenges on the same time from the amendments. The unregistered ethics committee (ECs) cannot legally review and accord their approval for clinical trials protocols, So EC have started applying and getting registered for legally review and accord their approval for clinical trials. On the other hand, investigator and their team, the sites EC and the site/institutional heads/chairman all have additional responsibilities as part of their scope. This has started amendments to informed consent documents and their submission to EC and licensing authority. The defined process within the fixed timelines to report adverse event and serious adverse events. Rule 122 DAB, this amendment to introduce the review and

circumstances that led to the SEA and accordingly determine the extent of negligence by each of the parties involved in the clinical trial. After that CDSCO has system for all SAE reports that are to be considered by the DCGI. The system has checklist for determining the acceptability of an SAE report in order to ensure that it contains all necessary administrative and technical information for ascertaining the nature and cause of the SAE, thereby allowing prudent determination of the quantum of compensation.

Amendments in schedule Y(2013)

In Feb 2013, the MoHFW established expert committees constituted for formulating guidelines, standard operating procedures and approval procedures have been provided recommendations with an effective policy document. The MoHFW has discussed the recommendations of the expert committee members (six members), In the meeting, all recommendations were clarified by the committee and after the meeting, the ministry in-principle accepted the recommendations of the committee.[10] The ethics committee of the institute and the principal investigator of the trial should be accredited.

The Drugs and Cosmetics (Amendment) Bill, 2013 was introduced on August 29, 2013 in the Rajya Sabha. The bill proposed changes in the regulation of the import, export, manufacture, distribution and sales of the drugs, cosmetics and medical devices and to ensure safety, efficacy, quality and conduct of clinical trials.

The new drugs definition is change i.e.[13]

- Not in significant use in India and not recognized as effective and safe by the Drugs Controller General of India.
- Approved by the DCGI for certain claims but are being marketed with modified/new claims
- A fixed dose combination of two or more drugs, which are individually approved but are being combined for to first time in a fixed/changed ratio
- All vaccines, recombinant Deoxyribonucleic acid derived product, living modified Organism, Stem cells, gene therapeutic product etc. which is intended to be used as drugs.
- Under the act, medical devices were covered under the definition of drugs. The bill changes this by adding a definition of medical devices to include ant instrument, implant, material or other article, including the software, intended to be used specially for human beings or animals for the specific purposes of diagnosis, prevention, treatment or

alleviation of any disease or, injury, modification of the body's anatomy and sustaining life.

- Clinical trials are defined in relation of drugs, cosmetics and medical and medical, and involve their systematic study with the objective of determining their safety, efficacy, performance or tolerance. Anyone initiating a clinical trial has to register with the central Drug Authority (CDA) and get approval from and ethics committee registered with it.
- The Central Government shall establish a CDA to subsume the existing Central Drugs Standards Control Organisation. The CDA will be composed of representatives from the Ministries of Health and Family Welfare, Law, Commerce and Industry, Science and Technology, Chemicals and Fertilisers, DCGI, Indian Council of Medical Research, Directorate General of Health Services, and other experts nominated by the central government, including those from state licensing authorities.
- The CDA shall among others, specify guidelines, structures and requirements for the effective functioning of the central and state licensing authorities; review, suspend or cancel any licence or permission issued by them; and decide on disputes between two or more state licensing authorities relating to the provisions of the Act and rules and regulations made under it.
- The DCGI is the central licensing authority that has the power to issue, renew, suspend or cancel licences for import, export or manufacture of drugs, cosmetics or medical devices or permission for conducting clinical trials. The DCGI also has the sole power to issue licenses for the manufacture, sale, and export of 17 categories of drugs.
- The Bill constitutes the Medical Devices Technical Advisory Board and the Drugs Technical Advisory Board to advise the central and state governments and the CDA on technical matters pertaining to medical devices, and drugs.
- In order to ensure standard quality of drugs, cosmetics, and medical devices, the Bill specifies conditions under which they will be considered misbranded, adulterated, and spurious and specifies penalties and offences for the same.

Amendments in schedule Y(2014)

The drug controller of India has issued circular to expert committee's making a wide range of changes to the agency's policies governing clinical trials on dated 03 Jul 2014.[14] CDSCO is also re-structure of the committees involved in the drug approval process. This was executed formulating policy and guidelines for the approval of new drugs, clinical trials and the banning of drugs.

New policies stated in the documents include

- Sponsors, investigators, the regulator and Ethics Committees are responsible for ensuring that the design of placebo-controlled trials is appropriate, efficient and ethical;
- Investigators are limited to working on a maximum of three trials simultaneously;
- If a new chemical entity is approved in the innovator or "well-regulated" country for a disease prevalent in India, and the clinical trial included Indian participants, CDSCO advises that "approval should be sought from CDSCO" and "these NCEs should be marketed in India speedily." CDSCO also specifies that if a foreign trial included Indian participants, the number would have to be "adequate" for considering approval of the drug in India;
- Waiver of clinical trials in Indian populations with drugs already approved outside India will only be considered in cases of national emergency, extreme urgency and epidemic, and for orphan drugs for rare diseases and drugs for conditions/diseases for which there is no therapy;
- Generics and biosimilars marketing "in other countries like USA" for over four years and have a "satisfactory report" can be approved in India after abbreviated trials;
- Consideration of new drug applications will take into account ethnic differences in metabolism etc.;
- If two or more countries remove a drug from their market on the grounds of safety and efficacy, the continued marketing of the drug in India "will be considered for examination and appropriate action" by CDSCO;
- Manufacturers, sponsors and CROs are advised to provide compensation for any drug-related anomaly detected at a later stage.

Amendments in schedule Y(2015)

In 09 Sep, 2015, Government of India has taken initiative to create an IT enabled system for online submission and processing of application as well as monitoring of clinical trials in the country. In order to improve transparency, accountability and efficiency in processing of clinical trial applications and it'smonitoring.

Amendments in schedule Y(2016)

The Central Drugs Standard Control Organization (CDSCO) in pursuance of Implementation of e-Governance has launched an online portal SUGAM on 14th Nov 2015. The portal is intended for e-filing applications for various services rendered by CDSCO. The e-filing of applications for Global Clinical Trials (GCT) Divisions was launched on 24th Oct 16. In this regard the applicants who have applied for approval of global clinical trials in 2016 and who have not received CT NOC's till date are requested to submit their applications in online mode (i.e; e-filing) for the stabilization/validation and the smooth transition to the e-system.

Amendments in schedule Y (2017): (Ministry of Health and Family welfare final G.S.R. 103 (E).

Whereas a draft of certain rules further to amend the Drugs and Cosmetics Rules, 1945 was published as required by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940) vide notification of the Government of India in the Ministry of Health and Family Welfare (Department of Health and Family Welfare) number G.S.R. 667 (E), dated the 5th July, 2016, published in the Gazette of India, Extraordinary, Part II, Section 3, Sub-section (i), dated the 5th July, 2016, inviting objections and suggestions from persons likely to be affected thereby before the expiry of a period of forty five days from the date on which the copies of the Official Gazette containing the said notification were made available to the public 5th July, 2016.

Now, therefore, in exercise of the powers conferred under section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Drugs and Cosmetics Rules, 1945, namely

(1) These rules might be called the Drugs and Cosmetics (4th Amendment) Rules, 2017.

(2) They should come into force on the date of their publication in the Official Gazette.

In the Drugs and Cosmetics Rules, 1945 (hereinafter referred to as the said rules), after rule 36, the following rule shall be inserted, namely: -

"36A Import of drugs by charitable hospital free of cost. — (1) Small quantity of drugs received in donation by a charitable hospital for the purpose of treatment of the patients in the said hospital may be imported provided the drugs are given or administered to the patients free of cost.

(2) The drugs shall not be prohibited for import and permitted to be marketed in the country with residual shelf life of one year or more."

In the said rules, in rule 45, in sub-rule (1), after the words "in accordance with these rules", the following words and the proviso shall be inserted, namely: -

"Within a period of sixty days of the receipt of the sample: Provided that where it is not possible to test or analyze the sample within the specified period, the Government Analyst shall seek extension of time from the Government giving specific reasons for delay in such testing or analysis."

In the said rules, in rule 91, for the words "one year from the date of issue", the words "three years from the date of issue" shall be substituted.

In the said rules, rule 124A shall be omitted.

In the said rules, in Schedule A, (a) in Form 11, in paragraph 3, for the words, "one year", the words "three years" shall be substituted; (b) in Form 29, in paragraph 3, for the words "one year", the words "three years" shall be substituted.

Amended Drugs and Cosmetic Draft Rules–Gsr 104(E) Released (2018)

The draft amendment of drugs and cosmetic rules as per GSR 104(E) has been released dated February 1, 2018. If any stakeholders reported any objections and suggestions within specified period of 45 days from the release date will be considered by the central government. This draft amended rule has contained 12 chapters and 8 schedules. Amended rules included orphan drug, Post trial access, accelerated approval process and validity of clinical trial permission was limited of 2 years. The main change in the amended rules were change in fee structure for all applications and clinical trial applications. Timelines for permission to conduct a clinical trial of a new drug already approved outside India have been specified as 90 days and compensation and medical management.

New Drugs and Clinical Trial Rules, 2019

Minister of Health and Family Welfare (MoHFW), India has published the new drugs and clinical trials rules 2019 on 19 March 2019 but applicable on 25 March 2019 onwards, except for Chapter IV, which should come into effect 180 days after publication in the Gazette, i.e. 180 days after March 19, 2019.The DCGI is commonly referred to as the Central Licensing Authority in the Indian regulations. Now Schedule Y is known as New drugs and Clinical Trials rules 2019.

These NDCT rules 2019 applied to all investigational New drugs for human use, new drugs, Clinical trial, bioequivalence study, bioavailability study and ethics committee. This NDCT rules superseded Schedule Y of drugs and cosmetics rule and Part XA with immediate effect. All existing licenses, orders, directions will continue to remain valid.

THE NEW DRUGS AND CLINICAL TRIAL RULES, 2019 CONTAINS 13 CHAPTERS AND 8 SCHEDULES

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- **Fifth Schedule:** Post Market Assessment
- **Sixth Schedule:** Fee Payable for License, Permission and Registration Certificate
- **Seventh Schedule:** Formula to Determine the Quantum of Compensation in the Cases of Clinical Trial related Injury or Death
- **Eighth Schedule:** Application for registration/renewal of Ethics Committee relating to clinical trial for BA/BE study or Biomedical Health research

Chapter I: Preliminary

In this chapter new definitions have been introduced for Clinical trial site, Biomedical and health research, Efficacy, GCP guidelines, Orphan drugs, Post trial access, registered pharmacist, similar biologic, Trial participants. According to NDCT rules new drugs means "A vaccine, r-DNA derived product, living modified organism, monoclonal anti body, stem cell, gene therapeutic product or xenograft intended to be used as drug".

"Biomedical & health research" means research including studies in basic, applied and operational research or clinical research designed primarily to increase scientific knowledge about disease and conditions (physical or socio-behavioral) their detection and cause; and evolving strategies for health promotion, prevention or amelioration of disease and rehabilitation but does not include clinical trial as per the definition of clinical trial.

"Post-trial access" means making a new drug or investigational new drug available to a trial participant after completion of clinical for a period deemed as considered necessary by investigator or the Ethics committee.

"Orphan drug" means a drug intended to treat a condition which affects not more than five lakh persons in India.

Chapter II: Authorities and Officers

The drugs controller General of India (DCGI) heads CDSCO, appointed by the central Government of India in the Ministry of Health Family welfare has been posted as the Central Licensing Authority under the NDCT rules, to act as the nodal entity for licensing and approvals under these rules.

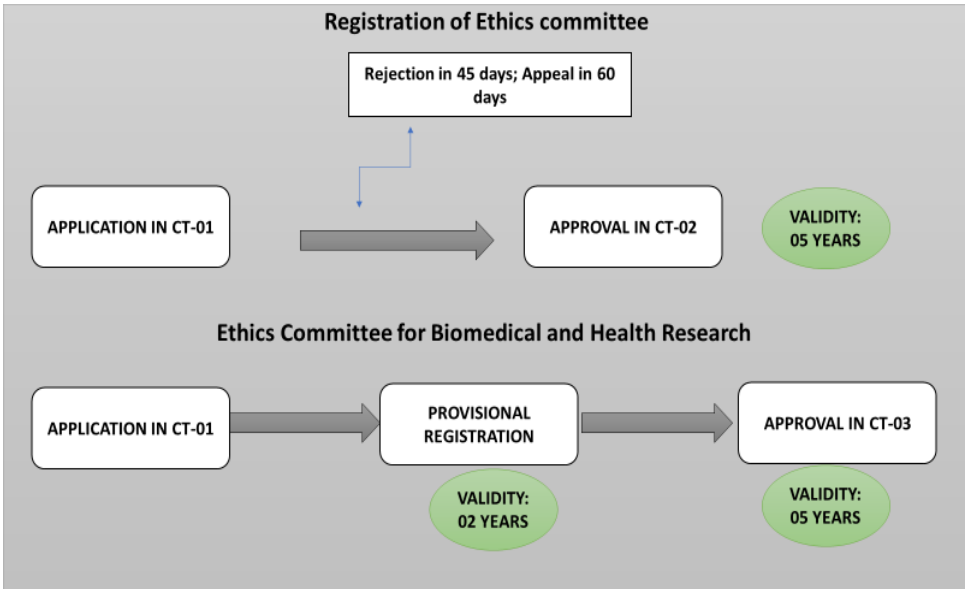
Chapter III: Ethics Committee for Clinical trial, Bioavailability and Bioequivalence Study

Under the NDCT Rules, an Ethics Committee is required to be registered under the Central Licensing Authority will be valid for a period of five years. An Ethics committee have minimum of seven members including medical, Non-Medical, scientific and Non-scientific area with one-woman member is mandatory; one lay person; one legal expert; one independent member from any other related field such as social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian. At least 50% members to be from outside the institute or organization in which EC is constituted. Every member of the EC shall be required to undergo such training and development programs as may be specified by the CLA from time to time.

CDSCO after scrutinizing documents furnished may grant registration to EC in form **CT-02 within 45 Days** of receipt of application. If EC is aggrieved by the decision of rejection of application**,** an appeal may bemade to the MoHFW within **60 days** of receipt of order of such rejection. Application for renewal if registration can be made 90 days before expiry and provided that fresh set of documents are not required to be furnished if there is no change in the documents submitted at the time of grant of registration. Only a certificate to this effect shall be rendered by the applicant. Application for renewal of registration to be made 90 Days prior to the date of the expiry of the registration and change in the membership to be intimated to DCGI within 30 working days.

Chapter IV: Ethics Committee for Biomedical and Health Research

Ethics committee for Biomedical and health research shall be required to register with the authority designated in department of health research under the central Government (MoHFW).



Chapter V: Clinical trial, Bioavailability and Bioequivalence Study of New Drugs and Investigational New Drugs.

1. **Part A:** Rule 21. Application for permission to conduct clinical trial on new drugs or investigational new drug.

- Application shall be made in form CT-04 & permission grant in Form CT-06
- In case of rejection, the applicant may request CDSCO to reconsider the application within 60 day from date of rejection on payment of fees as specified under rules.
- If applicant is aggrieved by the decision of rejection of application, an appeal may be made to the MoHFW within 60 days of receipt of order of such rejection.

2. Rule 23. Application for permission to conduct CT as part of discovery, research and manufacture in India.

- If the application made under rules 21 is for drugs which are discovered in India or R&D of drug is being done in India and also the drug is proposed to be manufactured and marketed in India, then such application shall be disposed off by CDSCO within a period of 45 days.

- Provided that where no communication has been received from CDSCO to the application within said period, the permission to conduct CT shall be deemed to have been granted by CDSCO and shall be deemed legally valid for all purposes.
- The applicant who has taken deemed approval should be before initiation a clinical trial informs CDSCO under Form CT-04A.
- On the basis of said information, CDSCO shall take on record the Form CT-04A which shall become part of official record and shall be called automatic approval of CDSCO.

3. Rule 24. Application for permission to conduct CT of a new drug already approved outside India.

- Such applications shall be disposed off by CDSCO within a period of 90 Days of receipt of the application by CDSCO.

4. Rule 25. Condition of permission of clinical trial

- Six monthly status report of each clinical trial, as to whether it is ongoing, completed or terminated shall be submitted to the central licensing authority electronically.
- The clinical trial shall be initiated by enrolling the first subject within a period of one year from the date of grant of permission, failing which prior permission from the central Licensing authority shall be required.
- Where a clinical trial does not have its own Ethics committee, Clinical trial at that site may be initiated after obtaining approval of the protocol from the registered institutional/Independent EC of another trial site provided that the approving Ethics committee shall in such care be responsible for the study at the trial site. Provided further that, the approving ethics committee and the clinical trial site or the bioavailability and Bioequivalence center, as the case may be, shall be located within the same city or within a radius of 50 KM of the clinical trial site.
- CDSCO shall be informed by applicant of EC approval of the study within 15 days of approval.

5. Rule 26. Validity period of permission of Clinical trial

- Clinical trial permission grated by CDSCO under Form CT-06 shall remain valid for period of 2 years from date of its issue unless otherwise. Also, under exceptional circumstances upon written request of applicant can be further extended for a period of 1 year.

6. Rule 27. Post- trial access of investigational new drug or new drug

- If investigator has recommended post-trial access of drug after completion of clinical trial to any trial subject and the same has been approved by the ethics committee, the post-trial access shall be provided by the sponsor of such clinical trial to the trial subject free of cost-
- If the clinical trial is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator.
- The trial subject or legal heir of such subject, as the case must be, has consented in writing to use post-trial investigational new drug or new drug; and the investigator has certified and the trial subject orhis legal heir, as the case must be, has declared in writing that the sponsor shall have no liability for post-trial use of new drug.

7. Rule 28. Academic clinical trial

- No permission for conducting CT on any drug is required from CDSCO where-
- Where the trial of permitted drug formulation is intended solely for academic research purpose.
- Clinical trial has been initiated after EC approval.
- The observation generated from CT are not required to be submitted to CDSCO.
- The observations generated from such CT are not used for promotion purpose.
- In the event of a possible overlap between the academic clinical trial and clinical trial or a doubt on the nature of study, the ethics committee concerned shall inform CDSCO in writing indicating its views within thirty days from the receipt of application on which CDSCO it shall be presumed that no permission is required from CDSCO in such cases.

8. **PART-B:** Rule 33. Application for permission to conduct BA/BE Study.

- Application for permission shall be made in Form CT-05 to CDSCO.

9. Rule 34. Grant of permission to conduct BA/BE Study.

- Permission shall be granted by CDSCO under Form CT-07 within 90 day.
- Provision of appeal to CDSCO (within 60 days) and to ministry (within 45 days) is there in case applicant is aggrieved by the rejection of application for permission.

10. Rule 35. Condition of permission for conduct of BA/BE study.

- BA/BE study id investigational new drug shall be registered with the clinical trial registry of India (CTRI) maintained by the Indian council of Medical Research before enrolling the first subject for the study.

- In case of termination of any BE/BE study, the detail reasons for such termination shall be communicated to CDSCO within thirty days of such termination.
- BA/BE study shall be initiated by enrolling the first subject within a period of one year from the date of grant of permission, failing which prior permission from the central licensing authority shall be required.

11. Rule 36. Validity of permission for conduct of BE/BE study.

- Permission shall remain valid for a period of one year from the date of issue unless suspended or cancelled by CDSCO.
- Also, under exceptional circumstances upon writing request of applicant, permission can be further extended for a period of 1 year.

Chapter VI: Compensation

1. Rule 40. Compensation in case of injury other than permanent disability in clinical trial or BA/BE Study.

- In the event of such injury, not being permanent in nature, the quantum of compensation shall be commensurate with the loss of wages of the subject.

2. Rule 41. Medical Management in Clinical trial or BA/BE study of new drug or investigational new drug.

- Clinical trial related injury/death/permanent disability: -Failure if investigational product to provide intended therapeutic effect where, the required standard care or rescue medication, though available, was not provided to the subject as per clinical trial protocol.

- SAE: Injury/ Injury-Permanent Disability/Death (Study- Related/ Not related)
  - Investigator- report all SAE within 24 hours of occurrence to CLA
  - Sponsor and the investigator- SAE reports within fourteen days of the

Knowledge of occurrence

- EC- SAE report along with opinion on compensation within a period of 30 days
- CLA forward the SAE reports Death or Permanent disability to Expert

Committee

- The expert committee make its recommendations for the cause of the SAE, Quantum of compensation and relatedness of death with study within 60 days
- The sponsor or its representative whoever taken permission shall pay the Compensation within 30 days of the receipt of order from CLA.

- In case of injury the sponsor shall provide free medical management as long as Required.

Death related to Clinical trial

Compensation = (B x F x R) / 99.37

B = Base amount (i.e. 8 lacs)

F = Factor depending on the age

R = Risk Factor (0.5 to 4)

0.5 terminally ill patients (survival less than 6 months)

1.0 Patient with high risk (survival between 6 to 24months)

2.0 Patient with moderate risk

3.0 Patient with mild risk

4.0 Healthy Volunteers or trial subject of no risk.

Injury related to clinical trial (other than death)

A permanent disability

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

D = Percentage disability

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

Congenital anomaly or birth defect

A fixed deposit of lump sum amount, monthly interest of which is Approximately half of minimum wage of the unskilled worker (in Delhi) e.g. 4 – 4.5 lakhs. In case of birth deformity or intervention need to provide Medical management and financial compensation

Chronic life-threatening disease and Reversible SAE in case it is

Resolved

Compensation = 2 x W x N

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

N = Number of days of hospitalization

Chapter VII: Bioavailability and Bioequivalence Study Centre

1. Rule 45. Application for registration of BA/BE study center.

- Application for registration of BA/BE center shall be made under Form CT-08.

2. Rule 47. Grant of registration of BA/BE study center

- Grant of registration in form CT-09 within90 days of application receipt.

3. Rule 48. Validity period and renewal of registration of BA/BE study center.

- The registration shall remain valid for a period of 5 years from the date of issue unless suspended or cancelled by CDSCO.
- Application for renewal of registration can be made three months before expiry and renewal shall be issued within 45 days.

4. Rule 49. Conditions of registration.

- In case of termination of any such study prematurely, the detailed reasons for such termination shall be communicated to CDSCO immediately.
- If there is any change in constitution or ownership of the BA/BE study center, the center shall intimate the change in writing to the CDSCO within thirty days of such change.

Chapter VIII: Manufacture of New Drugs or Investigational New Drugs for Clinical Trial, BA/BE study for examination, test and analysis

5. Rule 52. Application for permission to manufacture of new drug or investigational new drug for clinical trial or BA/BE study.

- Application shall be made in Form CT-10 to CDSCO for obtaining permission.

6. Rule 53. Grant of permission to manufacture of new drug or investigational new drug for Clinical trial and BA/BE study center.

- Permission shall be granted by CDSCO in Form CT-11 within period of 90 days of receipt of application. Permission remain valid for a valid for a period of three years from date of issue with a provision to extend further extension of 1 years.

7. Rule 56. License to manufacture of new drug or investigational new drug for clinical trial or BA/BE study.

- After obtaining permission to manufacture drug for clinical trial/BA-BE study under form CT-11, Rule 53, application for obtaining license to manufacture drugs for CT shall be accompanied with permission granted under Rule 53.

Chapter IX: Import of New Drugs and Investigational New Drugs for Clinical Trial or BA/BE Study or for examination, test and analysis

8. Rule 67. Application for import of new drug for clinical trial or BA/BE study.

- Application is made in Form CT-16 to CDSCO and license is granted in Form CT-17 within a period of 90 days of receipt of application.

- Provision of appeal exists in case of rejection of application for license.

Chapter XII: Miscellaneous

1. Rule 97. Pre-submission meeting.

- Any person intends to make an application for grant of license or permission for import or manufacture of new drugs or to conduct clinical trial may, request by making an application in writing, for a pre-submission meeting an with the CLA or any other person authorized by the CLA for seeking written guidance of such license or permission of manufacturing process, Clinical trial and other requirement after paying fees specified under sixth schedule.

2. Rule 98. Post-submission meeting.

- Appointment shall be sought by the applicant to discuss query if any raised by CDSCO within 15 days issue of such query after paying fees specified under sixth schedule.

3. Rule 101. Name of countries for purpose of new drug approval.

- DCGI will specify names of countries for considering waiver of local clinical trial for approval of drugs.

4. Rule 103. Debarment of applicant.

- Debarment for submitting misleading, or fake. or fabricated documents

5. Rule 104. Order of suspension or revocation in public domain.

- Any order of suspension or revocation or cancellation of any permission or license or registration, will be published on CDSCO website.

SCHEDULES

First Schedule (Rule 19 & 31**):** General Principles and Practices for Clinical Trial.

Second Schedule (Rule 21, 75, 80 & 97**):** Requirements and Guidelines for permission to Import or manufacture of New Drug for Sale or to Undertake Clinical Trial.

1. Provision for accelerated approval process

- Accelerated approval process may be allowed toa new drug for a new drug for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of alternative treatment, provided that there is a prima facie case of the product being if meaningful therapeutic benefit over the existing treatment.
- In such case, the approval if the new drug may be based on data generated in clinical trial where surrogate endpoints rather than using standard outcome measure such as survival

or disease progression, which are reasonably likely to predict clinical benefit, or a clinical endpoint.

- Post marketing trials will be required to validate the anticipated clinical benefit.
- Accelerated approval mat also be granted to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease of special relevance to the country, and addresses unmet medical needs.
- If the remarkable efficacy is observed with a defined dose in the phase II clinical trial of investigational new drug for the unmet medical needs of serious and life-threatening disease in the country, it may be considered for grant of marketing approval by the LA based in phase II clinical trial data. After approval to generate the data on larger population to further verify and described the clinical benefits.

2. Provision for quick or expeditious review process for approval of a new drug after clinical development

- In situation where the evidence for clinical safety and efficacy have been established even if the drug has not completed the all or normal clinical trial phases, the sponsor or applicant may apply to the licensing authority for expedited review process wherein the licensing authority will examine and satisfy the conditions as specified under clause 1 (2) (ii) (B) (i) of second schedule.
- If the sponsor or applicant may also apply to the licensing authority for expedited review process for mew drugs developed for disaster or defense use in extraordinary situation, such as was time, the radiation exposure by accident or intention, sudden deployment of forces at areas with higher risk, where specific preventive and treatment strategy is required, here new intervention in the form of new drug, route of delivery or formulation has been developed and were real life clinical trial may not be possible. The permission for manufacture of such new drug may be granted subject to conditions as specified under 1 (2) (ii) (B) (ii) of second schedule.
- The new drug is an orphan drug as defined is clause (x) of rule 2 of these rules.

Third Schedule (Rule 8, 10, 11, 25, 35, 42 &49): Conduct of Clinical Trial

1. Investigator brochure (Table 7)

- A format of investigator brochure has been included in rules. The format and content of the IB prescribed in the new rules is pretty much similar to existing format as per Indian as per Indian GCP appendix IV.

2. **Prescribing Information (Table 8)**

- A specific template has been provided for prescribing information under Table 8 of third schedule. Information like patient counseling information, details of manufacture, details of permission or license number with date are some additional requirements of PI document in the new rules.

Fourth Schedule: Requirements and Guidelines for conduct of BA/BE study of New Drugs or Investigational New Drugs

The requirement of BA/BE studies are explicitly prescribed under fourth schedule of the rules and clearly defined process for;

- General principle
- Maintain of records
- Retention of samples
- BA/BE study center
  - Organization and management
  - Documented SOPs
  - Clinical pharmacological Unit
- **TABLE 1**: Document required for registration of BA/BE center.
- **TABLE 2**: Data and information required for grant of permission to conduct BA/BE study of a new drug or investigational new drug.
- **TABLE 3**: Data and information required for grant of permission to conduct BA/BE study of a new drug already approved in the country.

Fifth Schedule (Rule 77 & 82): Post Market Assessment

1. **Phase IV [Post marketing] trial**

- Defined process & fees for approval of phase IV studies have been provided in the new rules and the phase IV study fees – INR 200,000.
- Including additional drug-drug interactions/dose-response/safety studies & trial designed to support use under the approved indication, e.g. mortality or morbidity studies etc.
- Such trial will be conducted under an approved protocol with defined scientific objective, inclusion and exclusioncriteria, safety efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population.

- In such trial the ethics aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provision including that for compensation in case of clinical trial related injury or death and GCP guideline.
- In such study, the study drug may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the drug free of cost.

2. Post marketing surveillance study or observational or non-interventional study for active surveillance

- Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package insert.
- The regulatory provision and guideline applicable for clinical trial of a new drug are not applicable.

Sixth Schedule (Rule 21, 22, 33, 34, 45, 47, 52, 53, 60, 67, 68, 75, 76, 80, 81, 86, 91, 97, & 98): Fee Payable for License, Permission and Registration Certificate

Sr.No.	Type of Application	Previous Fees	New Fees
1	Clinical trial Phase I	50,000 INR	300,000 INR
2	Clinical trial Phase II & III	25,000 INR	200,000 INR
3	Clinical trial Phase IV	No fees	200,000 INR
4	Reconsideration of clinical trial application	No fees	50,000 INR
5	BA/BE Study	25000 for drugs approved within 1 year & 1500for drug B/W 1 to years	200,000 INR
6	Reconsideration of BA/BE Study	No Fees	50,000 INR
7	Registration of BA BE study	No Fees	500,000 INR
8	Reconsideration of BA/BE center application	No Fees	500,000 INR
9	Permission to manufacture new drugs or investigational new drugs for clinical trial or BA/BE study	No Fees	5000 INR per product
10	Reconsideration of application to manufacture new drugs or investigational new drugs for clinical trial or BA/BE study	No Fees	2000 INR per product
11	Pre-submission meeting	No Fees	500,000 INR
12	Post-submission meeting	No Fees	50,000 INR

Seventh Schedule (Rule 39, 40 & 42): Formula to Determine the Quantum of Compensation in the Cases of Clinical Trial related Injury or Death

- No change as compared to exiting rules (age group 16 years and above)

- Need to develop formula for calculating quantum of compensation for age group < 16 years.

Eighth Schedule: Application for registration/renewal of Ethics Committee relating to clinicaltrial for BA/BE study or Biomedical Health research

Form	Rules	Subjects
CT-01	8, 10, 17	Application for registration/renewal of ethics committee relating to clinical trial or BA/BE study or Biomedical health research
CT-02	8, 9, 10, 14	Grant of registration of ethics committee relating to clinical trial or BA/BE study
CT-04	21	Application for grant of permission to conduct clinical trial of new drug or IND
CT-04A	23	Information to initiate clinical trial or new drug or IND as part of discovery, research and manufacture in India
CT-06	22, 25, 26, 29, 30	Permission to conduct clinical trial of new drug or IND
CT-16	67	Application for grant of license to import new drug or investigational new drug for the purpose of clinical trial or BA/BE study or for examination, test and analysis
CT-17	68, 69, 70, 71, 72	License to import new drug or investigational new drug for the purpose of clinical trial or BA/BE study or for examination, test and analysis
CT-24	86	Application for license to import of unapproved new drug for treatment of patient of life-threatening disease in a government hospital or government medical institution
CT-25	87, 88, 89, 90	License to import of unapproved new drug for treatment of patients of life-threatening disease in a government hospital or government medical institution.

Impact of Recent Regulatory Changes of Conducting Clinical Trials in India

The New Drug Clinical Trial Rules, 2019 has notified by Union Ministry for Health and Family Welfare with an aim/vision to promote clinical research in the country:

- Aim to providing predictable, transparent and effective regulation for clinical trials and by insuring the increasing accessibility of new drugs to the Indian population.
- Minimize the time for approving applications.
- In case of no communication from Drugs Controller General of India, the application will be deemed to have been approved, drug Controller General of India will decide the compensation in cases of death and permanent disability or other injury to a trial subject (Applicable in specific cases).

- The requirement of a local clinical trial may be waived for approval of a new drug if it is approved and marketed in any of the countries specified by the Drugs Controller General with the approval of the government.
- New drugs approved for use in select developed markets will be automatically allowed in India provided global trials include Indian patients.
- This waiver would also extend to drugs that receive these marketing approvals even while a trial is underway in India.
- New rules have **removed regulations on tests conducted on animals** in case of drugs approved and marketed for more than two years in well-regulated overseas drug markets.
- Minimize the time process: The speed of clinical trial depends on taking long time for regulatory approval and requirement of patient, number of investigator site reduced only registered ethics committee (EC) approved clinical trial protocol.
- Increase cost: The site cost per patient will increase as the investigator has to spend more time per recruited patient. The investigator has to devote time and effort to become aware of new regulatory compliance processes.
- Maintaining record and ready for inspection available for long monitoring and audit visit from sponsor team.
- The sponsor in addition to the above, the cost of medical management, and compensation for clinical trial related SAE, and exhaustive monitoring and audit will have a big impact on the trial budget.
- Ensuring quality and compliance: The regulatory inspections conducted to check good clinical practice (GCP) compliance have highlighted areas of deficiencies in quality. These regulatory inspection findings suggest that there are deficiencies in compliance to regulatory requirements for (1) Human protection and (2) data integrity, the EC's role has become crucial in ensuring rights, safety and wellbeing of the clinical trial participants EC should devote time and efforts in re-learning ethical issues - human protection, independence in decision making, handling conflict of interest, reviewing safety reports and compensation and effective oversight of clinical trial conduct during the trial conduct.

CONCLUSION

Clinical trial systematic study for discovering, generating, verifying the clinical and pharmacological profile/adverse effects of a new drug/molecule on human participants, before introduce drug in the market it is a only way to establishing the safety and efficacy of that particular molecule, as per regulatory the safety, well-being is the main criteria because

that drug is used to treat human-being. It is important for anyone initiating a trial of a new therapy in human participants that specific aims, problems and anticipated risks and benefits should be considered as per regulatory requirements and it should be scientifically sound and ethically justified. As per regulatory concern and the amendments are very essential for smoothly conducting or initiating the clinical trial, these changes should be made with the existing law to addressing or resolved the evolving issues. Since 2016 to last update of 19th Mar 2019 the Indian regulatory authorities have announced a spate of laws and guidelines, which will have a huge impact on the clinical trial sector in India, the NDCT rules were introduce over the Schedule Y of the D&C rules, the earlier rule was based on the "multiple stop gap measures" therefore the Indian attorneys believed that update these rules make more essential, the notification of a dedicated, comprehensive set of rules to regulate NDCT rules will lead to make greater clarity and synchronization in the regulatory requirements to initiate clinical trial in India. However, they believe there are still matters of concern. For example, the observation that the prescribed system of compensation for clinical trial participants could be perceived as an attempt of executive branch government to surpass its mandate and engage in the domain of the judiciary. D&C Act provisions preclude payment for compensation in such cases. This, exacerbated by the fact the Central Government is not empowered to make any rules prescribing compensation, as the relevant chapters where compensation rule-making apply silent on compensation. The net takes away from this law firm, The D&C Act is silent on the issue of compensation and the formula established in the NDCT Rules appear to expand beyond the actual D&C Act scope (e.g. encroaching into the terrain of the Judiciary). For the time being, this is the new legal reality governing the conduct of clinical trials in India.

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