Clinical Trials in India: Regulatory Updates

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Outline

- Scope
- Regulation of Biomedical and Health Research (BHR)
- EC for clinical trial
- EC for Biomedical and Health Research
- Compensation in case of CT and BHR
- Post trial access
- Timelines for CT application
- Import / manufacture of unapproved new drug
- Regulation of new drug
- Accelerated approval
- Post marketing Safety Assessment
- New GSR 354 (E) dated 05-6-2020, requirements for (CT-29) Import license of new drug and (CT-31) for manufacturing new drug for the compassionate use

Drugs & Cosmetics Act 1940

➢ Principle

The principle on which the Drugs & Cosmetics Act function is by a system of licensing under which all the activities involved in manufacture, sale and distribution of Drugs & Cosmetics are **controlled**.

➢ Drug Regulatory System in India

Drug is in concurrent list of Indian Constitution. It is governed by both Centre and State Governments under the Drugs & Cosmetics Act, 1940 and Rules 1945 thereunder.

Background Information on Indian NRA

- The Central Drugs Standard Control Organization (CDSCO) is the National Regulatory Authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act 1940 and Rules framed thereunder.
- Government of India is committed to a robust regulatory system for ensuring safety, quality and efficacy of Drugs. It has taken various initiatives, including revision of the existing regulatory framework and also committed nationally and globally to achieve all public health goals.
- Pharmaceutical Sector is one of the key 25 sectors identified by the Govt. of India under the ambitious Make in India initiative, which is likely to provide the necessary impetus to the sector in order to achieve its true potential and channel political commitment and resources in contributing towards robust drug regulatory system in India.

Drugs and Cosmetics Act

Preamble

To **regulate** manufacture, sale, distribution and import of drugs, cosmetics, Biologicals, medical devices and other products.

Objective

The Objective of Drugs & Cosmetics Act is to **ensure** that public are supplied with safety, efficacy and quality of drugs (Sec. 3b).

Basic Philosophy

The basic philosophy of Drugs & Cosmetics Act is that the **manufacturer is responsible for the quality** of drugs manufactured by them and the **Government/Regulatory Agencies will monitor** the quality of drugs by periodic inspections of the manufacturing and sales premises for confirmation to the provisions of Drugs & Cosmetics Act and monitoring the quality of drugs moving in the market by carrying out post market surveillance.

New drugs & CT Rules 2019

- Draft of New Drugs & CT Rules 2018 – GSR 104(E) dt: 01-02-2018
- WP (civil) No: 33/2012 & other WPC No: 79/2012 (Indore vs Union of India and swathaya Adhikar manch)
- System of supervision of CT
- **G.S.R.227(E) dt. 19.03.2019 -New Drugs and Clinical Trials Rules, 2019**
- These Rules have come in to force from the date of publication in the Official Gazette, i.e. from 19th March 2019 except Chapter IV, which shall come in to force after one hundred and eighty days and now it is also effectively implemented from19-9-2019.
- There are **107** Rules contained in **13** chapters and **8** Schedules. They shall apply to all New drugs, Investigational New Drugs (IND) for human use, clinical trial, bioequivalence study, bioavailability study and Ethics Committee.

CH. I : PRELIMINARY - Definitions

- **CT site:** Institute or hospital or any clinical establishment having required facilities to conduct CT
- **Effectiveness & Efficacy :** Ability to achieve desired effect
- **GCP :** Formulated by CDSCO & adopted by DTAB
- **API :** Any substance used in a FPP with intention to provide Pharmacological activity for diagnosis, treatment, mitigation/cure of disease; or
  : have direct effect in restoring, correcting or modifying Physiological functions in human beings or animals

- **Medical Management :** Treatment and necessary activities for providing medical care to complement the treatment

CH. I : PRELIMINARY - Definitions

- **NCE :** Not approved as a drug, proposed to be developed as new drug for the first time by establishing its safety & efficacy
- **IND** : Not approved for marketing as a drug in any country
- **Orphan drug:** A drug intended to treat a condition which affects ≤ 5 lac persons in India
- **PTA :** To a CT participant , after completion of trial based on benefit accrual during CT
- **PV :** Science & activities relating to detection, assessment & understanding & Preventing AE's or drug related problem

CH. I : PRELIMINARY - Definitions

- **AE :** Untoward medical occurrence resulting in death, permanent disability, hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, birth defect or life threatening event

- **Similar biologic :** Similar in terms of quality, safety & efficacy to reference biologic

- **Trial Subject :** Patient/healthy person to whom IP is administered for the purpose of CT

Definition of New Drugs [As per Rule 2(w)

- (i) A drug, including active pharmaceutical ingredient or **Phytopharmaceutical drug**, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made thereunder, as per conditions specified in the labeling thereof and has not been approved as safe and efficacious by the Central Licensing Authority with respect to its claims
- **Phytopharmaceutical Drug"** means a drug of purified and standardised fraction, assessed qualitatively and quantitatively with defined minimum **four bio- active or phytochemical compounds** of an extract of a **medicinal plant or its part**, for internal or external use on human beings or animals, for **diagnosis, treatment, mitigation or prevention of any disease or disorder** but **does not** include drug administered through **Parenteral route**

Definition of New Drugs [As per Rule 2(w)]

- (ii) Drug approved by the Central Licensing Authority for **certain claims and proposed to be marketed with modified or new claims** including indication, route of administration, dosage and dosage form
- (iii) a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form

(As per previous Definition under Rule 122(E) of Drugs and Cosmetics Rules, 1945)

New drugs definition----cont.

- (iv) **Modified or sustained** release form of a drug or **novel drug delivery system** of any drug approved by the Central Licensing Authority
- (v) 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
- The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs **for a period of four years** from the date of their permission granted by the Central Licensing Authority and the drugs referred to in sub-clauses (iv) and (v) shall **Always** be deemed to be new drugs; **[Drugs under sub-clauses (i), (ii) and (iii) will not be considered as "New Drug" after four Years from its date of Approval].**

- **As per Rule 2(S) Investigational new drug"** means a new chemical or biological entity or substance that has not been approved for marketing as a drug **in any country.**
- **Unapproved Drug (as per Rule 59):** Active pharmaceutical ingredient, which is not approved **under Rule 76** or **Rule 81** of the **Drugs and Cosmetics Rules, 1945**

Orphan Drug

- A drug intended to treat a condition which affects not more than five lakh persons in India

- No fee for conduct of clinical trial

- Provision for accelerated/expedited approval process

Biomedical and Health research (BHR)

- Earlier there was no regulation
- Now there is a separate Chapter (Chapter IV) for regulation of BHR
- Biomedical and health research" means research including studies on basic, applied and operational research or clinical research, designed primarily to increase scientific knowledge about diseases and conditions (physical or socio-behavioral); their detection and cause; and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation but does not include clinical trial as defined in clause (j);
- With effective from September 19, 2019
- BHR to be conducted in accordance with "**National Ethical Guidelines for Biomedical and Health Research involving Human Participants"** by ICMR.
- **EC for BHR** is required to be registered with DHR, MoH&FW
- Deals with Non regulatory Studies/Trials
- EC to oversee the study
- SAE & Compensation dealt by EC as per the BHR guidelines

CH. III : ETHICS COMMITTEE FOR CLINICAL TRIAL, BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

- Applicable Rules : 6 to 14
- Constitution
- Registration, validity, renewal

- Applicable Forms : CT-01 , CT-02 for registration & renewal
- Time lines 90 days.

Ethics Committee

Ethics Committee is a committee comprising of medical, scientific, non-medical and non-scientific members whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial and it shall be responsible for reviewing and approving the protocol the suitability of the investigators, facilities methods and adequacy of information to be used for obtaining and documenting informed consent of the study subjects and adequacy of confidentiality safeguards."

Ethics committee for Clinical Trial

- Deals with Regulatory CT as well as Academic CT & BA/BE
- Constitution- minimum 50% of members and Chairman from outside, MS from the institute
- SAE reporting timeline, causality and compensation as per CT Rules & Formula
- Compensation order for regulatory CT by DCGI
- Academic CT-compensation and other ethical issues as per "National Ethical Guidelines for Biomedical and Health Research involving Human Participants" by ICMR.
- Registration with CDSCO mandatory
- Registration is valid for 5 years (earlier 3 years)
- Members must be trained on Rules & GCP to safeguard Rights, Safety and wellbeing of trial subjects as may be prescribed by CLA
- If not trained, shall be disqualified.

Can accord approval to CT Protocol if-

- Constituted in accordance with Rule 7
- Located in same city or within 50 km radius of CT Site
- Takes the responsibility of patients rights, safety and wellbeing
- SAE reporting as per timeline in regulatory trial

EC involved in approving BHR well as CT and BA/BE studies

- Required to be registered with both
  - CDSCO for CT, and
  - DHR for BHR

CH. III : ETHICS COMMITTEE FOR CLINICAL TRIAL, BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

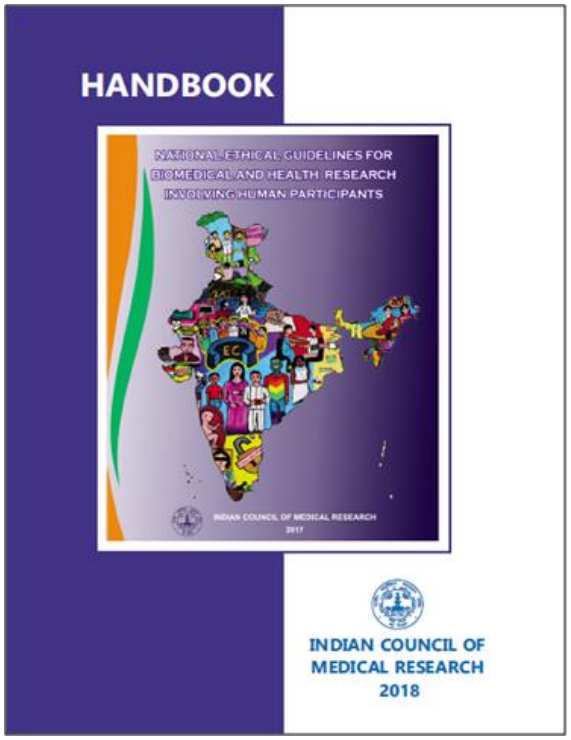
- **Suspension/ cancellation**
  - Failure to comply with the provisions
  - SCN, Personal hearing
  - CLA actions:
    - Withdraw show cause notice
    - Issue warning
    - Reject the results
    - Suspend/cancel
    - Debar members to oversee CT
    - Provision for appeal within 60 working days
  - Central Govt – May pass order within 60 working days

CH. IV : ETHICS COMMITTEE FOR BIOMEDICAL AND HEALTH RESEARCH

- Biomedical & Health Research : Research including studies on
  - ✓ Basic, applied & operational research or clinical research
  - ✓ To increase scientific knowledge about disease & conditions (physical/socio-behavioral)
  - ✓ their detection and cause
  - ✓ evolving strategies for health promotion & does not include clinical trial as defined in clause (j)
- Applicable Rules : 15, 16, 17, 18
- Forms : CT-01& CT-03
- Information & documents to be submitted : Table 1 of 3rd Schedule

CH. IV : ETHICS COMMITTEE FOR BIOMEDICAL AND HEALTH RESEARCH

- Provisional registration – for 2 years
- Final registration – CT-03 – 5 years
- Appeal within 60 working days to Central Govt.
- Renewal within 45 days
- Change in composition to be intimated



- Function, proceedings of EC, maintenance of records shall be as per National ethical guidelines for Biomedical & Health Research.

CH. IV : ETHICS COMMITTEE FOR BIOMEDICAL AND HEALTH RESEARCH

➢ Suspension/ cancellation

- ❑ Designated authority may show cause, & opportunity of being heard

- ❑ Actions that can be taken
  - Issue warning
  - Suspend/cancel
  - Debar its members to oversee any research in future for such period as considered necessary.

CH. VI : COMPENSATION

- Rules applicable :39 to 43
- Free medical mgt + Financial compensation as long as required for
  1. Death
  2. Injury other than death
     - Permanent disability
     - Non permanent injury
     - Injury to a child in utero due to participation of the parent

CH. V : CT, BA-BE STUDY OF NEW DRUGS & INDs
Part A: Clinical Trials

- **Suspension or Cancellation**
  - Show cause notice
  - Warning letter
  - Debar the sponsor/PI
  - Reject the results of CT
  - Suspend the CT-06/CT-4A

- Appeal within 60 working days

Academic clinical trial

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

Permission from CLA not required where-

- **The clinical trial on approved drug is intended solely for academic research purposes for-**

  -new indication or new route or new dose or new dosage form

- **Observation not for submission to CLA**
  - **Not for promotional purpose**
  - **EC approval required**
  - **Compensation will be as per National guidelines-ICMR**

Post-trial access of IND / new drug

Post trial Access means making a new drug or IND available to trial subject after completion of clinical trial through which, the said drug is beneficial to trail subject during clinical trial, for such period as considered by investigator and ethics committee.

- On investigators recommendation
- Where no alternative therapy is available
- No liability to sponsor for post-trial use (patient commits in writing).
- After approval by the Ethics Committee for clinical trial
- Free of cost by sponsor

Compensation

In case of injury in Academic CT and BHR

As per "National Ethical Guidelines for Biomedical and Health Research involving Human Participants" by ICMR:

- EC is responsible for relatedness of the SAE .
- EC should recommend appropriate compensation.

Compensation & Medical Management in case of CT

- In case of an injury , the sponsor, shall provide free medical management as long as required or till such time it is established that the injury is not related to the CT, whichever is earlier.
- If the death or the injury is related to CT, the compensation is payable as per the formula specified in the Schedule to the Rules.

Timelines for application of CT

A. In case of CT, as part of discovery, research and manufacture and marketing in India

- Permission /Rejection/Query in 30 working days

- Deemed approval, if no reply in 30 working days.

(However the applicant has to intimate CLA about initiation)

B. For other applications for CT

- Permission /Rejection/Query in 90 working days
- NO deemed approval provision

Import /Manufacture of unapproved new drug

IMPORT:

- Medical Officer of Govt hospital may import
- Approved for marketing in the country of origin
- For patients suffering:

  -From life threatening disease or

  -Disease causing serious permanent disability or

  -For unmet medical needs

MANUFACTURE:

- For treatment of patient of Serious/life threatening disease in Govt. Hospitals/ institution
- No satisfactory therapy available in the country
- Can be approved to be manufactured in limited quantity

Approval of New Drug

- Disposal of New drug applications within a period of 90 working days.
- Provision for Accelerated approval with condition of requirement of Post Marketing Trial
- Provision for application by Sponsor for Expedited Review
- In case of modified or new claims and NDDS the non clinical and clinical data requirement may be relaxed omitted under certain conditions.
- Permission /Rejection/Query in 90 working days

Accelerated Approval Process

Second Schedule of New Drugs and Clinical Trial Rules, 2019 deals with Accelerated Approval

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

- In such case, the approval of the new drug may be based on data generated in clinical trial where surrogate endpoint shall be considered.
- After granting accelerated approval for such drug, the post marketing trials shall be required to validate the anticipated clinical benefit.
- Accelerated approval may also be granted to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease of special relevance to the country, and addresses unmet medical needs.
- This provision is intended to facilitate and expedite review of drugs so that an approved product can reach the therapeutic armamentarium expeditiously.
- If the remarkable efficacy is observed with a defined dose in the Phase II clinical trial of investigational new drug for the unmet medical needs of serious and life threatening diseases in the country, it may be considered for grant of marketing approval by the Central Licensing Authority based on Phase II clinical trial data.
- In such cases, additional post licensure studies may be required to be conducted after approval to generate the data on larger population to further verify and describe the clinical benefits, as per the protocol approved by the Central Licensing Authority.

Accelerated Approval

- For serious/ life-threatening condition or disease, unmet medical needs/No alternatives available for a disease, taking into account its severity, rarity, or prevalence
- Surrogate endpoint shall be considered which are reasonably likely to predict clinical benefit
- Marketing approval may be based on Phase II clinical trial data, if remarkable efficacy observed in Phase II CT
- Phase IV CT mandatory to validate the anticipated clinical benefit.

Waiver of Local CT for approval of new drug

- If the new drug is approved and marketed in countries specified under the Rules and no major unexpected serious adverse events have been reported OR
- Global clinical trial which is ongoing in India AND
- No evidence, of

-difference in enzymes or gene, involved in metabolism

-factor affecting PK/PD, safety and efficacy of the new drug

Phase IV CT is required for such waivers. However the same may be relaxed under following conditions:

- Indicated in life threatening or serious diseases or diseases of special relevance
- For unmet need in India

  -XDR tuberculosis, hepatitis C, H1N1, dengue

  -Malaria, HIV, rare diseases

  -Orphan drug.

New Provisions for predictability of regulatory pathways

- Pre and Post- submission meeting
- The applicant can ask for Pre and Post-submission meeting with payment of fees.

To promote research by MSME & academic research:

- Fee for MSME 50% of the specified fee
- For Govt/ autonomous institution no fee for application to conduct CT

KEY ADVANTAGES OF NEW RULES

- Laid down clear pathway for new drugs, CT, BA/BE studies
- Make in India advantage to those who discover molecule in India with significant reduction in timelines CT deemed approval within 30 days.
- Reduction in approval timelines on par with global Regulatory agencies
- Online processing of all application as part of e-governance, ease of doing business

- Nearly 70 Million population in India suffer from rare disorders and many of which still not curable and their treatment is also very high.
- Moreover, the research in India is more skewed towards non-communicable diseases So, clinical trials in this field will bring much anticipated balance.
- The New rules and are expected to promote clinical research in the country through a transparent process yielding faster approvals.
- It is crucial to maintain highest standards as any compromise may jeopardize public confidence and participation in the clinical trials and may ultimately affect the availability of safe and effective products.

- The New rules state that any drug discovered in India or research and development of the drug has been done in India, and which is proposed to be manufactured and marketed in the country, will be deemed approved for clinical trials within 3 working days by Central Licensing Authority(CLA).
- In the event that there is no communication from the CLA to applicant within the stipulated time, then the permission to conduct clinical trial shall be assumed to have been granted.
- The DCG(I) would now accept the data generated outside the country thereby making the process easier and application time shorter.
- With digital revolution touching all the major-metros and mini-metros, patients can be monitored real time.

- The drug companies considering India as a market for running local clinical trials get additional benefits if the drugs are approved and marketed in the European Union, UK, Australia, Canada, Japan and US.
- The New rules will end the unnecessary repetition of trials and speed up the availability of New drugs in the country, lower the cost of drugs and will improve the ease of doing business for drug makers.
- To reap the benefits o clinical trials, our objective should be to bring about more clinical research in the country while maintaining high standards to ensure patient safety and accuracy of data.

- Compared to markets like
  - Indonesia where commuting is an issue, or
  - African countries where communication is a major problem or
  - Western Europe where the cost of trials are expensive and patients have limited health issues, but language is major barrier.
- India offers infrastructure, easy policies (in 2019) and the government has propensity to facilitate more companies considering Indian market as a ground for clinical trial.

Timeliness in Drug Regulatory System

- Reduced Application filing time
- Auto generated required Legal forms.
- Online Essential Document upload status

Process Re-engineering

- Inbuilt Pre Screening of Application .
- Inbuilt e-Office

Streamlined Scrutinizing of Application

- Ease in Application Scrutinizing coz no need to carry bulky files as the files are readily available within the system & Online query management

Increased Transparency

- Application Status will be available to the Applicant as well as CDSCO Officials at every level.
- National portal will monitor the status of clearances

Automation

- Auto Alerts will prompt the Officials to adhere to time lines for Application Scrutinizing.
- Permissions and Licenses will be generated automatically by system and instantly available to the Applicant.
- Legal Application forms will be generated automatically as prescribed in Drug Act.

The fruit of SILENCE is Prayer
The fruit of PRAYER is Faith
The fruit of FAITH is Love
The fruit of LOVE is Service
The fruit of SERVICE is Peace
Enjoy peaceful life

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Thank you