Drugs and Clinical Trials Rules, 2019

Context

- The Union Ministry for Health and Family Welfare has notified the Drugs and Clinical Trials Rules, 2019 with an aim to promote clinical research in the country.
- The new rules will change the regulatory landscape for the approval of new drugs and conduct of clinical trials in the country.
- These rules will be applicable to all new drugs, ethics committee and investigational drugs applicable for human use, bioequivalence studies and clinical trial in India.

Features of New Rules

- The new rules aim to **promote clinical research** in India by providing for a predictable, transparent and effective regulation for clinical trials and by ensuring faster accessibility of new drugs to the Indian population.
- New rules have **reduced the time for approving applications,** which has now come down to 30 days for drugs manufactured in India and 90 days for those developed outside the country.
- 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.
- 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.
- **Ethics committee will monitor the trials** and decide on the amount of compensation in cases of adverse events.
- It has been mandated that in case of injury to the clinical trial subject, medical management will be provided as long as required as per the opinion of the investigator.
- New drugs approved for use in select developed markets will be automatically allowed in India provided global trials includes Indian patients.
- This waiver would also extend to drugs that receive these marketing approvals even while a trial is underway in India.
- New rules has **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.

Clinical Trials

- A clinical trial is a systematic study to generate data for discovering or verifying the clinical and pharmacological profile (including pharmacodynamic and pharmacokinetic) or adverse effects of a new drug on humans.
- It is the only way of establishing the safety and efficacy of any drug before its introduction in the market for human use and is preceded by animal trials where the efficacy and side effects are observed in animals and an estimated drug dose is established.
- It is important for anyone preparing a trial of a new therapy in humans that the specific aims, problems and risks or benefits of a particular therapy be thoroughly considered and that the chosen options be scientifically sound and ethically justified.

Phases of Clinical Trials

- Clinical trials are carried out in four phases. Clinical trials of drugs developed in India have to undergo all four phases of trials in India.
- **Phase I or clinical pharmacology trials or "first in man" study:** This is the first time where the new drug is administered to a small number, a minimum of 2 healthy, informed volunteers for each dose under the close supervision of a doctor. The purpose is to determine whether the new compound is tolerated by the patient's body and behaves in the predicted way.
- **Phase II or exploratory trials:** During this phase, the medicine is administered to a group of approximately 10-12 informed patients in 3 to 4 centers to determine its effect and also to check for any unacceptable side effects.
- **Phase III or confirmatory trials:** Purpose is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. In this phase, the group is between 1000-3000 subjects. If the results are favorable, the data is presented to the licensing authorities for a commercial license to market the drug for use by the patient population for the specified and approved indication.
- **Phase IV trials or post-marketing phase:** Phase of surveillance after the medicine is made available to doctors, who start prescribing it. The effects are monitored on thousands of patients to help identify any unforeseen side effects.

Regulatory Mechanism in India

- Clinical trials in India are governed by the acts: **Drugs and Cosmetics Act, 1940, Medical Council of India Act, 1956 and Central Council for Indian Medicine Act, 1970.**
- Prerequisites of conducting a clinical trial in India are:
    - Permission from the Drugs Controller General, India (DCGI)
    - Approval from respective Ethics Committee where the study is planned
    - Mandatory registration on the ICMR maintained website

The Central Drugs Standard Control Organisation (CDSCO)

- CDSCO is under Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India is the National Regulatory Authority (NRA) of India.
- The **Drugs & Cosmetics Act, 1940** and **Rules 1945** have entrusted various responsibilities to central & state regulators for regulation of drugs & cosmetics.
- It envisages uniform implementation of the provisions of the Act & Rules made there under for ensuring the safety, rights and well being of the patients by regulating the drugs and cosmetics.
- CDSCO is constantly striving upon to bring out transparency, accountability and uniformity in its services in order to ensure safety, efficacy and quality of the medical product manufactured, imported and distributed in the country.
- Under the **Drugs and Cosmetics Act,** CDSCO is responsible for approval of Drugs, Conduct of Clinical Trials.
- It also lays down the standards for Drugs and has control over the quality of imported Drugs in the country
- It is also responsible for coordination of the activities of State Drug Control Organizations by providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.
- Further CDSCO along with state regulators, is jointly responsible for grant of licenses of certain specialized categories of critical Drugs such as blood and blood products, I. V. Fluids, Vaccine etc.

Key Issues with Clinical Trials

- 2013 Amendments to the Drugs and Cosmetics Act led to better protection of vulnerable groups but presence of ambiguous language is a concern.

- The big problem plaguing clinical research is an **over-representation of low-income groups among trial subjects**.
- Sometimes Clinical Research Organisations (CROs) recruit them selectively and exploit their ignorance. Their only reward from the trial is financial.
- Many times consent of the participants in the clinical trials is not taken.
- In most cases ethics committee is not constituted and people on such committees are not well trained.
- There is lack of independence for ethics committee working.
- There is need to register with Clinical Trials Registry of India for all clinical trials conducted in India. But registration is mostly done for positive trial cases. So there is lack of transparency.
- There are no well developed international standards dealing with clinical trials. India is a signatory of the **Declaration of Helsinki** but that is voluntary in nature and lack regulatory mechanisms.
- Three tier approval mechanisms has also led to delays in approval.
- Collusion between drug companies and doctors.
- Compensation for participating in research as well as research related injury is a major bone of contention these days.
- Moreover, regulatory failure and unethical clinical trials are also major issues.

Ethical Considerations

- The ethical issues in clinical research primarily involves:
    - Protection of Rights
    - Safety of subjects
    - Well being of the research participants
    - Informed consent and Voluntary Agreement of the participant.
    - Maintain privacy of the participant.
    - Accountability and transparency while conducting trials.
    - Research and trial details should be in public domain.

Significance of New Rules

- Near 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.
- 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 30 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.
- Removal of the compensation clause should be considered as a welcome move for all the subjects participating in clinical trials in India. Earlier there was no clarity and there were long and cumbersome legal hassles which created a question mark on the safety of trials.
- Besides the above change, 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, the UK, Australia, Canada, Japan and the US.
- The DCGI would now accept the data generated outside the country thereby making the process easier and application time shorter.
- Based on research the total number of clinical trials registered till Q1 2018 in India, the market might grow upto 8.5-9 per cent from 2019-2021 and then may pick up faster (2022-2026 to around >12 per cent, if the rules implemented in 2019, yields results in 2019-20 and saves time and cost for the multinational companies.

- Foreign companies based out of the US and Europe who have been eyeing China as a trial market are yet to gain confidence and are closely watching the scenario, post the new rule in 2019.
- Apart from this 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.

Criticism of New Regulations

- Monopolistic tendencies in the CRO market remains unaddressed.
- As India has the vast ethnic diversity the need of bridging trials for ethnically diverse populations to check drug suitability population is not addressed.
- Waiver should be only for drugs required urgently for national emergency.
- To prove a injury due to the trial is problematic and it is prone to manipulation.

Way Forward

- To reap the benefits of 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.
- A clinical trial should be planned and conducted by a trained investigator following the latest rules and regulations with meticulous record keeping and reporting.
- 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.
- With digital revolution touching all the major metros and mini-metros, patients can be monitored real time.
- 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.
- More and more mid and SME in the CRO segment should be incentivised to promote healthy competition and break down the monopoly. This will directly bring down the cost of conducting trials in India.
- Unless closely nurtured, this industry can lose its way and get entangled in the complexity of trials.