New Drugs and Clinical Trials Rules-2019: What academicians need to know

Sir,

The New Drugs and Clinical Trials Rules 2019, released by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health and Family Welfare (MOH & FW), Government of India, became effective from March 25, 2019, except Chapter 4 (*Ethics Committee for Biomedical and Health Research*), which became effective after 180 days (i.e. Sep 21, 2019).[1] The new rules (Rule 97 (Rule 122DAA)) supersede existing Part XA and *Schedule Y* of Drugs and Cosmetics Rules, 1945. However, all existing licenses, orders and directions will remain valid.

These rules shall apply to clinical trials, bioavailability or bioequivalence (BA/BE) studies of new drugs and regulation of ethical committees approving them. The primary objectives of the new rules are:

1. Promotion of research and development in India
2. Faster accessibility to new drugs
3. Predictability and transparency in approval process
4. Improvement data credibility and accuracy.

Table 1 highlights major changes in the new rules. Some of the key changes are given below:

1. For the first time, *orphan drug* has been defined as one intended to treat a condition affecting less than five lakh people in India. Clinical trial fee has been waived off for such drugs along with the provision of fast-track approval
2. To promote indigenous drug development, the timelines of approval process has been defined as 30 days. If no objection/query is raised by the CDSCO, the application will be considered "approved"
3. Provision of post-trial access has been made for patients if the new drug is deemed effective without any alternative. This will be provided free of cost by the sponsor.
4. It is now clarified that any type of study involving human subjects, except drug trials (as defined in clause J), will be governed by the National Ethical

Table 1: Major changes in Drugs and Clinical Trial Rules, 2019

Major changes	Summary
Clinical trial rules	Timelines defined for disposal of CTA
	90 working days
	30 working days if the CT is part of discovery, research and manufacture in India. If no response is received within 30 working days, the CTA would be deemed to be approved
	Validity of CT permission
	Study to be initiated within 2 years of CT approval (1 year for Bioavailability or Bioequivalence (BA/BE) study) being issued
	If not started within 2 years (or 1 year for BA/BE study), one must sek extension.
	Post trial access
	Provisions for providing the investigational drug to the trial subjects after completion of clinical trial, if found beneficial, with the recommendations of the ethics committee and the investigator
	No liability on sponsor
	Drug to be given free of cost
	Ethics committees
	For CT and BA/BE study
	To be constituted under rule 7 and registered under rule 8
	50% members from outside
	Registration valid for 5 years versus 3 years previously
	For Independent EC - should be within same city or within a radius of 50 km from the site
	For BHR
	Earlier there was no regulation
	Constituted under rule 16 and registered under rule 17
	Effective from 19 September 2019
	Need to follow ICMR 2017 guideline on "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants"
	No regulatory approval required; EC to oversee the study
	SAE and compensation as per IEC recommendation in line with ICMR guidelines
	Conditions of permission for conduct of CT
	DCGI and IEC NOC in place
	EC approval to be notified within 15 working days → if an IEC rejects the proposal, the sponsor must inform the DCGI office before applying to another IEC for the same site
	Notify study termination within 3 months
	If study drug is found beneficial, sponsor should apply for marketing authorization
	Compensation and medical management
	No major changes introduced in the process. The formulae used for arriving at the compensation amount for CT/BA-BE Studies has been included in the Rules
	Compensation for Academic or BHR - Will be as per ICMR guidelines
	Suspension or cancellation of CT permission in case of non-compliance
	After giving an opportunity of being heard
	Issue warning in writing describing the deficiency or defect observed, which may affect adversely the right, or well- being of a trial subject or the validity of clinical trial conducted
	Reject the results of clinical trial
	Suspend for such period as considered appropriate or cancel the permission granted
	Debar the investigator or the sponsor including his representatives to conduct any clinical trial in future
	Manner of labeling for investigational new drug
	Name of the drug or code number
	Batch or lot number, date of manufacture, use before date, storage conditions
	Name of the institution
	Name and address of the manufacturer
	The purpose for which it has been imported
	Label cannot be obliterated/altered without prior approval

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Table 1: Contd...

Major changes	Summary
New drug registration rules	Unmet need (definition)
	An unmet medical need is a situation where treatment or diagnosis of disease or condition is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs)
	Orphan drug (definition)
	An "orphan drug" means a drug intended to treat a condition which affects not >5 lakh persons in India
	Local clinical trial waiver for marketing authorization
	'(i) the new drug is approved and marketed in countries specified by the Central Licencing Authority under rule 101 and if no major unexpected serious adverse events have been reported; or
	(ii) the application is for import of a new drug for which the Central Licensing Authority had already granted permission to conduct a global clinical trial which is ongoing in India and in the meantime such new drug has been approved for marketing in a country specified under rule 101; and
	(iii) there is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug; and
	(iv) the applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the Central Licensing Authority
	Provided that the Central Licensing Authority may relax this condition, where the drug is indicated in life threatening or serious diseases or diseases of special relevance to Indian health scenario or for a condition which is unmet need in India such as XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, HIV, or for the rare diseases for which drugs are not available or available at a high cost or if it is an orphan drug.'
	Accelerated approval process
	Marketing approval based on remarkable Phase 2 study results
	For serious/life threatening disease or condition, considering its severity, rarity, or prevalence and the availability or lack of alternative treatments
	Surrogate endpoint shall be considered rather than using standard outcome measures
	Post approval study mandatory to validate the anticipated clinical benefit
	Expert committee
	SEC review is now a legal process
	SEC calendar posted → more predictability now in meetings and outcomes are getting posted quickly on CDSCO website
	Timeline for disposal of application
	90 working days (need to work in advance for preparation of executive summary and SEC presentation)
	If questions raised, post response revert within 90 days
	Two levels of appeal process if application rejected
	Pre submission and post submission meetings
	Pre submission - INR 5 Lakh
	Post submission - INR 50,000/-
	Post marketing safety assessment
	Phase IV
	As per the directive of DCGI office
	Requires protocol approval by DCGI
	All provisions of CT rules apply
	Study drug to be provided free of cost
	PMS
	Requires DCGI approval
	Should be aligned to approved indication and the PI
	No requirement to provide drug free of cost
	Provisions of CT rules not applicable
	PSUR submission
	Cumulative data to be provided for both India and worldwide
	For vaccines, rDNA products - to be submitted lifelong of the product

DCGI: Drug Controller General of India, ICMR: Indian Council of Medical Research, IEC: Institutional Ethics Committee, CTRI: Clinical Trial Registry of India, BHR: Bio-medical and Health Research, SAE: Serious adverse effect, CT: Clinical trial, PSUR: Periodic Surveillance Update Report, PMS: Post marketing surveillance, SEC: Subject Expert Committee, NOC: No objection certificate, CDSCO: Central Drugs Standard Control Organization, CTA: Clinical Trial Agreements, EC: Ethics Committee, PI: Principal Investigator

Guidelines for Biomedical and Health Research Involving Human Participants, 2017 formulated by the Indian Council of Medical Research (ICMR).[2] Compensation for any study-related serious adverse events will be decided by the Institutional Ethics Committee (IEC)

5. CDSCO registration is now mandatory for all IECs to approve regulatory clinical trials. However, accreditation by National Accreditation Board for Hospitals and Healthcare Providers – Quality Council of India (NABH–QCI) is not mandatory, although recommended. For approving non-regulatory trials, all IECs, should be registered with Department of Health Research (MOH & FW).

These new rules are expected to streamline processes for conducting clinical research in India. Provisions like longer renewal period for IEC registrations and waiver of local clinical studies are a welcome step. However, clarification is required regarding provisions like bridging trials for ethnically diverse subject population and regulatory role of the Drug Controller General of India (DCGI), if any, in areas like biomedical and health research, formation of IEC or compensation clauses.

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Conflicts of interest
There are no conflicts of interest.

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