New Drugs and Clinical Trial Rules, 2019

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MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health and Family Welfare)

NOTIFICATION

New Delhi, the 19th March, 2019

Legal Applicability

CHAPTER XII

AMENDEMENTS OF DRUGS AND COSMETICS RULES, 1945

97. In the Drugs and Cosmetics Rules 1945, after rule 122DA the following new rule shall be inserted, namely:—

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

Key Highlights

- **New Drug and Clinical Trial Rules, 2019** are applicable from date of release, 25th Mar 2019, except Chapter 4 *[Ethics Committee for Biomedical and Health Research],* which will come into force after 180 days (i.e. 21st Sep 2019)
- **Rule 97 (Rule 122DAA):** New Rules supersede existing Part XA and Schedule Y of D&C Rules, 1945
- All **existing licenses**, orders, directions will continue to remain valid
- **Defined timelines** for review and approval of CT applications:
  - ✓ 90 days for global clinical trials
  - ✓ 30 days for INDs being developed in India - If no response from DCGI, "*automatic approval*" to proceed, by notification to DCGI via Form CT-4A
- **Application fee** for Phase 1 to 4 clinical trials increased 6-8 folds

Key Highlights

- **Validity of Clinical Trial approval** for two years to "*initiate the study*" (extendable by one year)
- Two types of **Ethics Committees** (EC) defined:
  - ✓ for Clinical Trials & BA/BE studies
  - ✓ for Biomedical & Health Research
- Validity of EC registration increased to 5 years (*from 3 years*)
- DCGI to be informed about the approval granted by the EC within 15 working days of the grant of such approval
- In case of rejection of CT application, the applicant may request to reconsider the application within a period of 60 days from the date of rejection of the application
- **Quarterly report** of enrolment status to be submitted DCGI
- **Six monthly status report** (in place of annual status report) of each clinical trial
- **Termination** of study to be notified within 30 days

Key Highlights

- Provision of **Pre- and Post-submission meeting** with DCGI
- Provision of **waiver of local clinical trials**, if drug is approved and marketed in certain countries
- No change in process and requirement for Payment of **Compensation**
- Onus of providing medical management to the subject on the Investigator
- Conditions for **post-trial access** of study drug to trial participants outlined
- **EC Accreditation** is not mandatory
- SAE reporting timeline changed for sponsor : 14 calendar days from “awareness of SAE/Death” and not “Occurrence/onset of SAE.”
- PSUR content & structure is aligned with EU PBRER (ICH) format which is very detailed & exhaustive but timeline is retained as per old regulation as “30 calendar days” from data lock point.
- Free medical care – PI can decide to continue medical care Or until it is decided as not related

CHAPTER I: PRELIMINARY

Rule	Title	Change	Impact - Comments
2	Definitions	Includes new & revised definitions – *Academic clinical trial – new* *BA-BE studies – integrated in the rules* *Efficacy/effectiveness - new* *New drug – minor modification* *Orphan drug - **affects not more than 5 lakh population*** *Phytopharmaceutical drug - new* *Post-trial access - new* *Similar biologic - new* *Sponsor – modified* *..and others*	*Brings in more clarity* *Clinical Research Organization (CRO) has not been defined*** *CT applicant is considered as Sponsor*

**** NOTE: MDR 2017 clearly defines CRO:**
Medical Device Rules 2017 G.S.R. 78(E) dt 31 Jan 2017; Chapter I Preliminary, (3) Definitions, (o)
"clinical research organization" means any entity to whom a sponsor may transfer or delegate one or more of its functions and duties regarding conduct of clinical investigation or clinical performance evaluation;

Clinical Trial

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

(i) clinical or;

(ii) pharmacological, including pharmacodynamics, pharmacokinetics or;

(iii) adverse effects,

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

Orphan Drug

"**orphan drug**" means a drug intended to treat a condition which affects **not more than five lakh persons in India**;

Post-trial Access

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

New Drug

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 labelling thereof and has **not been approved** as safe and efficacious by the Central Licencing Authority with respect to its claims; or

ii. a drug **approved** by the Central Licencing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or

iii. a fixed dose combination of two or more drugs, 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; or

iv. a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or

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

Explanation: 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 Licencing Authority; and the* ***drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs;***

New Drugs and Clinical Trial Rules, 2019

CHAPTER III: ETHICS COMMITTEE FOR CLINICAL TRIAL, BA-BE STUDY

Rule	Title	Change	Impact - Comments
7	**Constitution of Ethics Committee for clinical trial**	Significant changes in the constitution of EC: • Minimum of seven members from medical, non-medical, scientific and non-scientific areas with at least, **one lay person; one woman member; one legal expert; one independent member from any other related field such as social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian**. • At least 50% of members not affiliated with the institute or organization in which EC is constituted • Every member of the EC shall be required to undergo such training and development programs	*Several Ethics Committees may have to be re-constituted to comply to the rules* *Should not impact ongoing studies*
9	**Validity period of registration of ECs for clinical trial**	• Validity of registration increased to 5 years	*Less cumbersome process of renewal of registration for ECs*

CHAPTER III: ETHICS COMMITTEE FOR CLINICAL TRIAL, BA-BE STUDY

Rule	Title	Change	Impact - Comments
10	**Renewal of registration of ECs for clinical trial**	Application for renewal of registration to be made 90 days prior to the date of the expiry of the registration	*Will allow ECs to continue to be functional for a longer period if the renewal application is submitted on time*
12 (4)	**Proceedings of ECs for clinical trials**	Any change in the membership or the constitution to be intimated to DCGI within 30 days days	*Maintaining compliance*
13	**Maintenance of records by ECs for clinical trial**	More comprehensive requirements for maintenance of records by ECs – Five years after completion of clinical trial	*ECs may have to undergo training and revise their SOPs*
14	**Suspension or cancellation of registration of EC**	Show cause notice / warning letter / rejection of results / suspension / debarment	*Wherever ECs fail to comply to the Rules*
15	**Ethics Committee for Biomedical and Health research**	Introduction of specific rules for ECs pertaining to biomedical research *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, ICMR to be followed*	*Impact on academic institutions to re-vamp existing ECs.* *May have to constitute separate ECs for clinical trials and academic research*

CHAPTER V: CLINICAL TRIAL, BA/BE STUDY OF NEW DRUGS & INDs

PART A: CLINICAL TRIALS

Rule	Title	Change	Impact - Comments
21	**Application for permission to conduct clinical trial of a new drug or investigational new drug**	Form CT-04 (in place of Form 44) with revised application fee as per Sixth Schedule *(Central/State Govt sponsored projects are exempt from application fee)*	*According to an Order issued by CDSCO on 10th Apr 2019, Form CT-04 (and other Forms) can be manually completed and uploaded in SUGAM, till all the new Forms are integrated into the online submission portal.* *No delays in submissions*
22 (2)	**Grant of permission to conduct clinical trial**	Decision on application will be taken within 90 working days	*Timelines for review of application now specified in the rules*
22 (3) (ii)	**Grant of permission to conduct clinical trial**	In case of rejection, the applicant can request the DCGI to reconsider the application within a period of 60 working days from the date of rejection of the application, on payment of fee	*Process to appeal and reconsideration of rejected application in place.*

CHAPTER V: CLINICAL TRIAL, BA/BE STUDY OF NEW DRUGS & INDs

PART A: CLINICAL TRIALS

Rule	Title	Change	Impact - Comments
23	**Permission to conduct clinical trial of a new drug or IND as part of discovery, research & manufacture in India**	"Automatic approval" For products being developed indigenously, the applications to conduct clinical trials will be considered approved if there are no queries raised by DCGI within 30 days of the application. The sponsor will have to just notify in Form CT-4A to DCGI prior to initiation of the clinical trial	*Welcome step to encourage new drug development in India!*

CHAPTER V: CLINICAL TRIAL, BA/BE STUDY OF NEW DRUGS & INDs

PART A: CLINICAL TRIALS

Rule	Title	Change	Impact - Comments
25 (ii)	**Conditions of permission for conduct of clinical trial**	Clinical trial sites that do not have their own EC, can use registered EC of another trial site; or an (registered) independent EC, that is located within the same city or within a radius of 50 kms of the clinical trial site	*Opens access to several new clinical trial sites for conducting trials*
25 (vii)	**Conditions of permission…**	Status of enrolment of the trial subjects shall be submitted to the DCGI on quarterly basis	*Increased notifications to DCGI and compliance*
25 (viii)	**Conditions of permission…**	Six monthly status report of each clinical trial to be submitted to DCGI (in place of Annual Status Reports)	*Increased notifications to DCGI and compliance*
25 (ix)	**Conditions of permission…**	Termination of clinical trial has to be notified within 30 days to the DCGI	*Compliance*

CHAPTER V: CLINICAL TRIAL, BA/BE STUDY OF NEW DRUGS & INDs

PART A: CLINICAL TRIALS

Rule	Title	Change	Impact - Comments
26	**Validity period of permission to initiate a clinical trial**	The **permission to initiate clinical trial** (under Rule 22) in Form CT-06; or "automatic approval" (under Rule 23) in Form CT 4A, will be valid for a period of 2 years from the date of its issuance (unless extended by DCGI)	*Clinical trial has to be initiated within 2 years of the issuance of the CT permission*
27	**Post-trial access of IND or new drug**	Post-trial access of drug to patients is completely at the discretion of the Investigator and approval by EC- drug has to be provided free-of-cost by the Sponsor	***No liability for post-trial use of investigational new drug or new drug on the Sponsor,*** *if the legal heir of the patient has consented the use of the new drug in writing.*
28	**Academic clinical trial**	No permission for conducting an academic clinical trial by DCGI, if it is intended for intended solely for academic research purposes. Only EC approval is mandatory. Observations of such clinical trial should not used for promotional purposes	*ICMR Guidelines to be followed* *Helpful in conducting academic research by various institutes and colleges*

CHAPTER VI: COMPENSATION

- No significant change in payment of compensation in case of clinical trial-related injury or death
- No change in the process of determination of causality assessment
- Minor (practical) change in safety reporting process

Rule	Title	Change	Impact - Comments
40	**Medical Management in clinical trial or BA/BE study of new drug or IND**	Sponsor to provide free medical management to the subject as long as required "**as per the opinion of investigator",** or till such time it is established that the injury is not related to the clinical trial, whichever is earlier	*Clarity on the decision on the requirement of medical management to be provided by the Sponsor* *Onus on the Investigators to decide whether Sponsor will pay for medical management or not.*
42	**Procedure for compensation in case of injury or death during clinical trial, BA-BE study**	(2) & (3) Cases of SAEs of death, permanent disability or any other injury other than death; shall be examined in the following manner, namely: *-- the sponsor or its representative and the investigator shall forward their reports on SAE of death after due analysis to DCGI, HOI, EC within fourteen days of the "**knowledge of occurrence of SAE of death**"*	*Changed form the 'day of occurrence of SAE' to 'knowledge of occurrence of SAE'.* *More practical approach*

CHAPTER IX: IMPORT OF NEW DRUGS & IND FOR CLINICAL TRIAL / BA-BE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Rule	Title	Change	Impact - Comments
73 (2)	**Manner of labelling**	Labeling requirements specified – no change in basic requirements **New labeling requirement:** where a drug is being imported by the licencee, on behalf of another person (sponsor), the licencee shall indicate on the label of the container the "name and address of the importer"	*Name and address of the Importer on Record (IoR) has to be on the drug label.* *For studies where a local representative (eg. CRO) of global pharma are the applicants (IoR), labels will have to be modified accordingly.*
73 (3)	**Manner of labelling**	Relabeling or any alteration of the IP label would require approval from DCGI	*Timelines for approval not specified – needs some clarification from DCGI*

CHAPTER X: IMPORT OR MANUFACTURE OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

Rule	Title	Change
73 (7)	**Application for permission to import new drug for sale or distribution**	**Local clinical trial (data) may not be required** to be submitted along with the application, if: i. the new drug is approved and marketed in countries and if no major SUSARs ii. 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; and iii. there is no probability or evidence, of difference in Indian population iv. undertaking in writing to conduct Phase IV clinical trial 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.
73 (8)		Submission of requirements relating to animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for more than two years in other countries

CHAPTER XIII: MISCELLANEOUS

Rule	Title	Change	Impact - Comments
98	**Pre-submission meeting**	Application, with fee to be submitted In the pre- or post-submission meeting, the DCGI or any other authorized person, shall provide suitable clarification to the applicant	*Not specified whether the "suitable clarification" will be verbal or written*
99	**Post-submission meeting**		
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 new drugs	*This decision is not a blanket one, and it is left to the discretion of the DCGI to provide waiver for local trials on case-to-case basis*
103	**Debarment of applicant**	Debarment for submitting misleading, or fake, or fabricated documents	*Compliance*
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	*Compliance*

SCHEDULES

- **FIRST SCHEDULE (Rules 19 & 31):** General Principles And Practices for Clinical Trial

- **SECOND SCHEDULE (Rules 21, 75, 80 and 97):** Requirements and Guidelines for Permission to Import or Manufacture Of New Drug for Sale or to Undertake Clinical Trial

Rule / Table	Title	Comments
Rule 1 (2)	Special situations for a new drug where relaxation, abbreviations, omission or deferment of data may be considered. **(A) Accelerated Approval Process** (B) Situations where quick or **Expeditious Review Process** can be sought for approval of a new drug after clinical development (applicable for Orphan Drugs)	*To be allowed to a new drug for a disease, depending on severity, rarity, or prevalence and the availability or lack of alternative treatments* *Although, post marketing trials shall be required for validation of clinical benefit*
Table 4	Data to be submitted along with application to conduct clinical trial or import or manufacture of Phytopharmaceutical drug in the country	*New specific requirements for Phyto-pharmaceuticals introduced*

SCHEDULES

- **THIRD SCHEDULE (Rules 8, 10, 11, 25, 35, 42 and 49):** Conduct of Clinical Trial

  - No change in the requirements of conducting clinical trials, informed consent, responsibilities of various stakeholders
  - Sponsor to provide **post-trial access of the IP** free of cost to the trial subject as per directions of DCGI under special circumstances on the recommendations of the PI and EC
  - No change in Informed Consent Form (**Table 3**)
  - Change in Investigator Undertaking (**Table 4**) – *template needs to be revised*
  - "*Appendix XI*" is now **Table 5** – *No change in the elements of SAE reporting*

- **FIFTH SCHEDULE (Rules 77 and 82):** Post-Market Assessment

  - *Distinction between Phase 4 trials and Post-Marketing Surveillance (PMS) studies*
  - *Not clear whether **Non-interventional/Observational studies** would also require approval from DCGI – **still a grey area***
  - ***PSURs** submission mandatory – defined structure of PSUR content & structure, now aligned with EU PBRER (ICH) format which is very detailed and exhaustive. Although the timeline for submission to DCGI is still is retained as '30 calendar days', and meeting this short timeline could be challenging.*

SCHEDULES

- **FIFTH SCHEDULE (Rules 77 and 82):** Post-Market Assessment

Phase IV (Post marketing) trial:

- **I**nclude additional drug-drug interactions/dose-response/safety studies & trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc.
- **Such trials will be conducted under an approved protocol** with defined scientific objectives, inclusion and exclusion criteria, safety efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population.
- In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions **including that for compensation** in case of clinical trial related injury or death and good clinical practices guidelines.
- 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

Post Marketing surveillance study or observational or non-interventional study for active surveillance:

- Such studies are conducted with a new drug under approved conditions of its use **under** a **protocol approved by DCGI,** with scientific objective. I/E of subject decided per prescribing information/approved package insert.
- Study drugs are the part of treatment of patient in the wisdom of the prescriber included in the protocol.
- **Regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable** in such cases as drugs are already approved for marketing

SCHEDULES

- **SIXTH SCHEDULE (Rules 21, 22, 33, 34, 45, 47, 52, 53, 60, 67, 68, 75, 76, 80, 81, 86, 91, 97 and 98):**
  Fee payable for license, permission and registration certificate

S. No.	Rule	Subject	INR
1	21	Application for permission to conduct clinical trial	
		Phase I	3,00,000
		Phase II	2,00,000
		Phase III	2,00,000
		Phase IV	2,00,000
2	22	Reconsideration of application for permission to conduct clinical trial	50,000
3	67	Application for import of new drugs or investigational new drugs for clinical trial or BA/BE study or for examination, test and analysis	5000 per product

SCHEDULES

- **SIXTH SCHEDULE (Rules 21, 22, 33, 34, 45, 47, 52, 53, 60, 67, 68, 75, 76, 80, 81, 86, 91, 97 and 98):**
  Fee payable for license, permission and registration Certificate

S. No.	Rule	Subject	INR
4	68	Reconsideration of application for Import of new drugs or investigational new drugs for clinical trial or BA/BE study or for examination, test and analysis	1000
5	98	Pre-submission meeting	5,00,000
6	99	Post-submission meeting	50,000
7		*Any other application which is not specified above*	50,000

- ✓ **No fee shall be chargeable in respect of application for conduct of clinical trial for orphan drugs**
- ✓ In case of application received from Micro Small Medium Enterprises (MSME) firms for conduct of clinical trial, approval of new drug and pre and post submission meeting, the fee payable shall be half of the fee specified above

SCHEDULES

- **SEVENTH SCHEDULE (Rules 39, 40, and 42):** Formulae to determine the quantum of compensation in the cases of clinical trial related injury or death

✓ **No change as compared to existing rules (age group 16 years and above)**

✓ **Need to develop formula for calculating quantum of compensation for age group < 16 years**

SCHEDULES

- **EIGHTH SCHEDULE: FORMS**

Form	Rule(s)	Subject
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-4A	23	Information to initiate clinical trial of 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 patients 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