International Journal of Clinical Trials
Annapurna SA et al. Int J Clin Trials. 2020 Nov;7(4):278-284
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: http://dx.doi.org/10.18203/2349-3259.ijct20204486

Review Article

New drug and clinical trial rules, 2019: an overview

Swathi A. Annapurna*, Srinivasa Y. Rao

Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India

Received: 03 September 2020
Revised: 11 October 2020
Accepted: 13 October 2020

***Correspondence:**
Swathi A. Annapurna,
E-mail: swathi.kodukula@gmail.com

ABSTRACT

Clinical trials are indispensable to the drug development method to confirm the effectiveness and safety of any new drug. India has undergone a big restrictive transformation about clinical trials. Numerous establishments taking part in a distinguished role in guiding the trial in India embody DCGI, DBT, ICMR, CBN, RCGM and GEAC. The government notified the new drugs and trial rules on 19 March 2019, to supersede part XA and schedule Y of the drugs and cosmetics rules 1945. Updating our knowledge about these is of utmost importance in today's turbulent scenario that prevails in the pharmaceutical industry. Thus, this review gives an idea about the recent changes regarding the regulations of clinical trials.

Keywords: Clinical trials, New drug, BA/BE studies, Pre-submission meeting, Post-submission meeting

INTRODUCTION

India's ministry of health and family welfare (MoHFW) has published the ultimate version of the latest drugs and clinical trials rules, 2019.[1-3] The new regulations cover provision for promoting clinical research also as complex topics like an orphan drug, post-trial access, and pre- and post-submission meeting.

The new rules appear comprehensive, well balanced, and certain to enhance the moral and quality standards of clinical trials in India, which can further benefit patients and industry. The approval for clinical trials in 30 working days for indigenous drugs also will speed up the trial process and encourage local drug development.

Today, general supposition in India isn't exactly for CTs-as a few contract research organizations (CROs) have been accused for directing preliminaries without due concern for procedural and moral issues.[4] Some more laws having a bearing on pharmaceutical manufacture, distribution and sale in India are the industries (development and regulation) act, 1951, the trade and merchandise marks act, 1958, the indian patent act, 1970 and the design act, 2000 and the factories act, 1948.[5,6]

Provision for accelerated product approval under some conditions, especially pre and post-submission meetings with authorities may add increased predictability and confidence within the system. However, shortened review timelines will definitely require additional manpower at the central drugs standard control organization (CDSCO) to make sure timely review of applications.

The newly published new drugs and clinical trials rules, 2019 are going to be referred to as new rules, 2019 during this article. The new rules are structured around 13 chapters which include 107 rules and eight schedules. The new rules will apply to all or any new drugs, investigational new drugs, orphan drugs, phytopharmaceutical drugs, clinical trials, biomedical and health research, and ethics committees. The new rules will override part XA and schedule Y of medicine and cosmetics rules, 1945, and enter effect immediately. Earlier regulations and schedule Y will still be applicable for veterinary use drugs.

The draft of these rules was published on February 1, 2018, and the government gave 45 days for comments and suggestions.[7] In September 2018 the supreme court at the behest of swasthya adhikar manch asked the Government to give more time for parties to comment on the rules.[8,9] In response of the SC's perceptions and headings, the Indian regulator, the central drugs standard control organization (CDSCO) presented a huge number of measures, some of which have been accused for a noteworthy drop in the quantity of clinical trials being led in India, with both domestic and foreign companies moving to alternate clinical trial sites. In March 2019, the government finally notified the new drugs and clinical trial rules 2019.[10,11]

The new regulations are also aimed toward promoting clinical research within the country by implementing a time-bound review of applications, allowing increased predictability and transparency of regulatory pathway and providing clarity on many complex subjects, including post-trial access. After a series of media allegations of unethical practices, in 2013 the CDSCO office made stricter regulations for conducting clinical trials.

Despite changes implemented to beat challenges in those regulations, much work was still required, evidenced by the very fact that the amount of clinical trials approved by the Indian regulator has still not yet reached the amount existing before 2013. To overcome the challenge of reduced clinical research in India, CDSCO revisited the principles on clinical trials and new drugs and introduced new drugs and clinical trials rules, 2019.

Earlier only one form was there for the application of new drug and IND that was the form 44. In these new drug and clinical trial rule, there are around 27 forms which are for the different purposes.

HIGHLIGHTS IN THE 2019 NEW DRUGS AND CLINICAL TRIALS RULES

Amendements of drugs and cosmetics rules, 1945

In the new drug and clinical trial rules 2019, rule 97 includes 122DAA in the drugs and cosmetic rules 1945 which consists of non-application of certain rules for new drugs and investigational new drugs for human use. Part XA and schedule Y shall not be applicable with regard to new drugs and investigational new drugs for human use.

New definitions in NDCT rules 2019

New drug clinical trials rules 2019 describes rule 2(a) as academic clinical trial as 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 licencing authority or regulatory authority of any country for marketing or commercial purpose.[3]

New drug clinical trials rules 2019 describes rule 2(h) "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-behavioural); their detection and cause; and evolving strategies for health promotion, prevention or amelioration of disease and rehabilitation but does not include clinical trial.

New drug clinical trials rules 2019 describes Rule X "orphan drug" means a drug intended to treat a condition which affects not more than five lakh persons in India.

New drug clinical trials rules 2019 describes Rule CC "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. The latest definition of new drug is given in Rule W as shown in the (Table 1).

The arrangement of the new drugs and clinical trial rules 2019 is easy to remember and logical. The rules are divided into chapters and each chapter refers to one aspect of research (Table 2 to Table 12).

Table 1: New drug

Definition of new drug	Statement
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; 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 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	These drugs shall continue to be new drugs for a period of four years from the date of their permission granted by the central licencing authority.

Continued.

Definition of new drug	Statement
A modified or sustained release form of a drug or novel drug delivery system of any drug approved by the central licencing authority; or 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;	These drugs shall always be deemed to be new drugs

Table 2: Ethics committee for clinical trial.[3]

Rule	Title for ethics committee for clinical trail	Change made in the new drug and clinical trial rules 2019
7	Constitution of ethics committee for clinical trial.	7 members one lay person; (ii) one woman member; (iii) one legal expert; (iv) 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.
8	Registration of ethics committee.	application made in form CT-01.
9	Validity period of registration.	five years from the date of its issue, registration granted in form CT-02.
10	Renewal of registration.	90 days prior to the date of the expiry of the registration.
12(4)	Proceedings.	Any change in the membership or the constitution intimated within 30 working days to CLA.
13	Maintenance of records.	**5** years after completion of every clinical trial or bioavailability study or bioequivalence study.
14	Suspension or cancellation.	show cause notice/issue warning letter /rejection of results/suspend for such period.

Table 3: Clinical trial, bioavailability and bioequivalence study of new drugs and investigational new drugs, part A clinical trial.[3]

Rule	Title for clinical trial, study of new drugs and investigational new drugs	Change made in the new drug and clinical trial rules 2019
21	Permission to conduct clinical trial of a new drug or investigational new drug.	Form CT-04 in place of form 44 (D & C act).
22(2)	Grant of permission to conduct clinical trial.	Decision shall be taken within 90 working days.
22(3)(ii)	Grant of permission to conduct clinical trial.	Reject the application within a period of 90 days reckoned from the day when the required information and documents were provided.
23	Permission to conduct clinical trial of a new drug or investigational new drug as part of discovery, research and 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.
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.
25 (vii)	Conditions of permission for conduct of clinical trial.	Status of enrolment of the trial subjects shall be submitted to the DCGI on quarterly basis.

Continued.

Rule	Title for clinical trial, study of new drugs and investigational new drugs	Change made in the new drug and clinical trial rules 2019
25 (viii)	Conditions of permission for conduct of clinical trial.	Six monthly status report of each clinical trial to be submitted to DCGI (in place of annual status reports).
25 (ix)	Conditions of permission for conduct of clinical trial.	Termination of clinical trial has to be notified within 30 days to the DCGI.
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).
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.

Table 4: Part B bioavailability and bioequivalence study.[3]

Rule	Title for bioavailability and bioequivalence study of new drugs and investigational new drugs	Change made in the new drug and clinical trial rules 2019
33	Application for permission.	Application in form CT-05.
34	Grant of permission.	Application in form CT-07 if not satisfied reject the application, for reasons to be recorded in writing within a period of 90 working days from the date of receipt of the application in form CT-05.
36	Validity period of permission.	Valid for a period of one year from the date of its issue.

Table 5: Compensation.[3]

Rule	Title for compensation in case of injury during clinical trials BA/BE study of new drug or IND	Change made in the new drug and clinical trial rules 2019
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.
42	Procedure for compensation in case of injury or death during clinical trial, BABE study.	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" of receipt of the application in form CT-05.

Table 6: Bioavailability and bioequivalence study centre.[3]

Rule	Title for bioavailability and bioequivalence study centre	Change made in the new drug and clinical trial rules 2019
45	Application for permission.	Application in form CT-08.
47	Grant of permission.	Application CT-09 within a period of 90 working days from the date of receipt of its application.
48	Validity period of permission.	Valid for a period of 5 year from the date of its issue.

Table 7: Manufacture of new drugs or investigational new drugs for clinical trial, bioavailability or bioequivalence study or for examination, test and analysis.[3]

Rule	Title for manufacture of new drugs or investigational new drugs for clinical trial, bioavailability or bioequivalence study or for examination, test and analysis	Change made in the new drug and clinical trial rules 2019
52	Application for permission.	Application in form CT-10.
53	Grant of permission.	Application CT-11 within a period of 90 working days from the date of receipt of its application.
54	Validity period of permission.	Valid for a period of 3 year from the date of its issue.
59	Application for permission to manufacture unapproved active pharmaceutical ingredient for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.	Application for manufacturer of pharmaceutical formulation in form CT-12 and manufacturer of the active pharmaceutical ingredient in Form CT-13.
60	Grant of permission to manufacture unapproved active pharmaceutical ingredient for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.	Manufacturer of pharmaceutical formulation in form ct14 and form CT-15 to manufacture the unapproved active pharmaceutical ingredient.
61	Validity period of permission.	Valid for a period of 3 year from the date of its issue.

Table 8: Import of new drugs and IND for clinical trial/BA-BE study or for examination, test and analysis.[3]

Rule	Title for import of new drugs and IND for clinical trial/BA-BE study or for examination, test and analysis	Change made in the new drug and clinical trial rules 2019
67	Application for permission.	Application in form CT-16.
68	Grant of permission.	Application CT-17 within a period of 90 working days from the date of receipt of its application.
69	Validity period of permission.	Valid for a period of 3 year from the date of its issue.
73 (2)	Manner of labelling.	Labelling requirements specified no change in basic requirements New labelling 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".
73 (3)	Manner of labelling.	Relabeling or any alteration of the IP label would require approval from DCGI.

Table 9: Import or manufacture of new drug for sale or for distribution.[3]

Rule	Title for import or manufacture of new drug for sale or for distribution	Change made in the new drug and clinical trial rules 2019
75	Application for permission.	Application in form CT-18.
76	Grant of permission.	Permission to active pharmaceutical ingredient for sale or for distribution in form CT-19 or pharmaceutical formulation for sale or for distribution in form CT-20 within a period of 90 working days from the date of receipt of its application.
80	Application for permission to manufacture new drug for sale or distribution.	Application for grant of permission to the central licencing authority in form CT-21.
81	Grant of permission for manufacture of new drug for sale or distribution.	Grant permission to manufacture new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-22 or pharmaceutical formulation for sale or for distribution in Form CT-23.

Table 10: Import or manufacture of unapproved new drug for treatment of patients in Government hospital and Government medical institution.[3]

Rule	Title for import or manufacture of unapproved new drug for treatment of patients in government hospitals and Government medical institutions	Change made in the new drug and clinical trial rules 2019
86	Application for import.	Application in form CT-24
87	Grant of licence for import.	Grant licence for import of an unapproved new drug by Government hospital and Government medical institution in form CT-25.
91	Application for permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease.	After obtaining the recommendation of the ethics committee, the manufacturer shall make an application in form CT-26.
92	Grant of permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease.	Grant permission in form CT-27.

Table 11: Miscellaneous.[3]

Rule	Title	Change made in the new drug and clinical trial rules 2019
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.
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.
103	Debarment of applicant.	Debarment for submitting misleading, or fake, or fabricated documents.
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.

Table 12: Increased fees for various applications.[3]

Rule	Subject	INR
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
22	Reconsideration of application for permission to conduct clinical trial.	50,000
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

Government organizations are not required to pay fees to conduct clinical trials. Similarly, for micro small medium enterprises (MSME), a 50% concession in application fees is available for conducting clinical trials, approval of new drugs, pre-submission meetings, and post-submission meetings. For conducting clinical trials for orphan drugs application fee is not charged.

Although the rise of application fee in some cases is extremely steep, it's additionally true that the fee amounts had not been revised for an awful while. The increased fees will be justified if they help the government in supplementing the costs associated with the expected increase in manpower, assisting the regulator in a faster review of an ever-increasing number of applications.

CONCLUSION

Clinical trials are considered as the key tools in new drug evaluation. Overall, the new rules will further benefit patients and industry but are comprehensive, well-balanced, and will likely improve the ethical and quality standards of clinical trials in the country. In order to speed up the clinical trial process and to encourage drug development, the approval for clinical trials in 30 working days for local drugs. Provision for accelerated product approval under some conditions, together with the provision of pre and post-submission with the CDSCO office, would add certainty and confidence within the system.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. Lavu Rathaiah, chairman Vignan group of institutions for providing online facilities to carry out the above review.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Ministry of health and family welfare (1940) the drugs and cosmetics act and rules. Available at: https://cdsco.gov.in/opencms/opencms/en/Acts-Rules/. Accessed on 20 July 2020.
2. CDSCO, ministry of health and family welfare (2001) good clinical practice: guidelines for clinical trials on pharmaceutical products in India, New Delhi. Available at: https://cdsco.gov.in/opencms/opencms/en/Clinical-Trial/clinical-trials/. Accessed on 20 July 2020.
3. New drugs and clinical trials rules, 2019, ministry of health and family welfare, India. Available at: http://www.egazette.nic.in/WriteReadData/2019/200759.pdf. Accessed 19 July 2019. Accessed on 20 July 2020.
4. Clinical trials in India. Available at: http://www.theweek.in/health/cover/clinical-trials-research-india.html. Accessed on 20 July 2020.
5. Guidance for industry on preparation of common technical document for import/ manufacture and marketing approval of new drugs for human use. Available at: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadGazette_NotificationsFiles/CTD%20Guidance%20Final.pdf. Accessed on 20 July 2020.
6. Application for grant of permission to import or manufacture a new drug or to undertake clinical trial. Available at: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/New-Drugs/Checklist/Update_ Checklist_10July2018.pdf. Accessed on 20 July 2020.
7. New drugs and clinical trials rules. Available at: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdfdocuments/NewDrugs_CTRules_2019.pdf. Accessed on 20 July 2020.
8. The supreme court order regarding the draft drugs and clinical trials rules. Available at: http://www.indiaenvironmentportal.org.in/content/458635/order-of-the-supreme-court-of-india-regarding-the-draftdrugs-and-clinical-trials-rules-2018-12092018/. Accessed on 20 July 2020.
9. Swasthya adhikar manch vs. union of India, written petition. Available at: https://www.casemine.com/judgement/in/58117eca2713e179478bb3d4. Accessed on 20 July 2020.
10. Uncertainty on approvals sees exodus of clinical trials. Available at: http://www.livemint.com/Industry/bQu4EtyMUgkAXEuDade3YN/Uncertainty-on-approvals-sees-exodus-of-clinical-trials.html. Accessed on 20 July 2020.
11. Biocon forced to move clinical trials out of India. Available at: http://www.businessstandard.com/article/companies/bioconforced- to-move-clinical-trials-out-of-india-114012400052_1. html. Accessed on 20 July 2020.

Cite this article as: Annapurna SA, Rao SY. New drug and clinical trial rules, 2019: an overview. Int J Clin Trials 2020;7(4):278-84.