Case Report

New Drug and Clinical Trial Rules 2019- Two Steps Forward and One Back

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ABSTRACT

The government notified the New Drugs and Clinical Trial Rules on 19th March 2019, to replace Part XA and Schedule Y of the Drugs and Cosmetics Rules 1945. Many new desirable changes have been made and these will help clinical research and trials in India. However, there are discrepancies which offset some of the advantages offered by the new rules. Including timelines for many regulatory functions, is among the main advantages offered, but incorrect use of terms, duplication of rule numbers is likely to complicate the regulatory procedures. The changed classification of Ethics Committees is a welcome feature, but it is unclear why the composition recommended by ICMR is accepted for the EC for Biomedical and Health Research, but not for the one for Clinical Trials, Bioavailability and Bioequivalence Studies. The government would do well to consider the suggestions made herein and amend the New Drugs and Clinical Trial Rules 2019.

Key words: New Drugs, Clinical Trials, Ethics Committee, Compensation, Amendments.

INTRODUCTION

Clinical research in India is regulated both by ethical guidelines and research regulations and both of these overlap in a number of situations. Ethical guidelines have not seen many changes in the recent past, but clinical research regulations have been recently changed. Schedule Y was introduced in the Drugs and Cosmetic Rules of 1945, almost 30 years ago. It survived for this period, though it went through at least two major amendments and numerous revisions, to finally move out of the rule book on 19th March 2019. It was a historic document, since for the first time, it laid down the procedures to introduce new drugs in the country. Prior to its introduction, new drug introduction was haphazard and unpredictable, at the hands of the powers that be.

Reverse engineering was the main strength of the Indian Industry then and any new drug cleared by the FDA, would be synthesized in India at a fraction of its cost and launched in the market. Schedule Y was brought in to regulate the launch of such molecules. The schedule brought in 1988, required Phase III clinical trials before a new drug could be launched in India, but this rule applied only for the first manufacturer who launched it, the followers were allowed to introduce the same molecule after demonstration bioequivalence of their formulation with that available abroad.[1]

A major amendment to Schedule Y[2] was necessitated following the publication of the ICH Guidelines,[3] and India's entry into the TRIPS agreement.[4] With this amendment, Schedule Y was brought on par with ICH GCP. Yet this was not sufficient, a series of new rules were brought in, in 2013 and these were followed by regular amendments.[5] Among these were two important rules, which made the audio-video recording of the consent process mandatory[6] and required accreditation of Ethics Committees.[7] Despite the fact that the government has asked the Drugs Controller to make accreditation by NABH mandatory, there is no clear-cut instruction to this effect from CDSCO.

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Now, the Schedule Y along with Part XA of the D and C Rules have been replaced by the New Drugs and Clinical Trial Rules 2019. The draft of these rules was published on February 1, 2018 and the government gave 45 days for comments and suggestions.[8] 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.[9] In March 2019, the government finally notified the New Drugs and Clinical Trial Rules 2019.

Careful study of the rules shows that changes are very few, but the arrangement and presentation of the rules has changed significantly. If one were to evaluate whether the new rules are better than the earlier ones and honest answer would be that, it is a mixed bag. Some changes are for the better, but some new problems have cropped up. To analyse the new rules it might be better to deal with the positive and negative points separately and this could be used by the authorities to make further amendment and improvement to the rules.

Improvements over the previous Rules

Arrangement

The original rules were arranged in a rather odd manner, with little logic. Take Rule 122 as an example. There were numerous sections of the rule, devoted to different aspects of clinical trials, but no logic is discernible. The sections of the rule were as follows:

122: Substances specified in Schedule C (1)

122 A: Application for permission to import new drug

122 B: Application for approval to manufacture new drug

122 C: Omitted

122 D: Permission to import or manufacture fixed dose combination.

122 DA: Application for permission to conduct clinical trials for New Drug/Investigational New Drug

122 DAA: Definition of a clinical Trial (now omitted)

122 DAB: Compensation in case of injury or death during clinical trial

122 DAC: Permission to conduct clinical trial

122 DB: Suspension or cancellation of Permission/ Approval

122 DC: *Appeal*

122 DD: Registration of Ethics Committee

There was no logical way to remember these rules and one had to depend on memory to do so.

The arrangement of the New Drugs and Clinical Trial Rules 2019 is very logical and easy to remember. The Rules are divided into Chapters and each chapter refers to one aspect of research.

Chapter I – Preliminary

Chapter II – Authorities and Officers

Chapter III – EC for Clinical Trials, BA and BE Studies

Chapter IV – EC for Biomedical and Health Research

Chapter V – Clinical Trials, BA and BE Studies on Investigational/New Drugs

Chapter VI - Compensation

Chapter VII – BA/ BE Centre

Chapter VIII – Manufacture of new drugs for CT, BA and BE studies

Chapter IX – Import of new drugs for CT, BA and BE studies

Chapter X – Import of new drug for sale or distribution

Chapter XI – Import or Manufacture of new drug for treatment in Government hospitals

Chapter XII – Amendment of Rules

Chapter XIII – Miscellaneous

All definitions have been grouped together and arranged alphabetically in section 2 of Chapter I. Similarly, there are seven schedules each dealing with a particular heading, making searching of information very easy.

Ethics Committees

There were two types of ethics committees in the past, Institutional and Independent. As per the registration letters, Institutional ECs had wide powers to review and approve clinical trials, bioavailability and bioequivalence studies. The powers of Independent ECs were limited to the review and approval of BA/BE studies only. Officials on different fora said that Independent ECs could review and approve biomedical and health research, but this was

never officially acknowledged in any document.

Under the new rules, ECs are divided into two types, those for Clinical Trials, BA and BE studies and those for Biomedical and Health Research. Thus, the authorities have recognized and acknowledged the need for EC approval of biomedical and health research. Mechanisms for registration have also been laid down, though presently no mechanism exists for the registration of EC for biomedical and health research, hence the entire chapter dealing with this type of ECs has been held in abeyance for 180 days.

Additional improvements are that the validity of registration of the EC has been increased from 3 years to five years, thus the frequency of the re-registration exercise reduces. Every EC has to inform the DCGI of any approval granted to a research proposal within 15 days of granting the approval. Additionally, timelines are provided within which registration will be granted or refused by the authorities, so also a method for appeal and redress has been defined.

Timelines

For the first time, the drug rules define timelines for receiving response from the regulators. The given timelines may not please all stakeholders and they can be improved. Promising a timeline during which a particular job will be completed is a conceptual advance in government work. Some tightening of the timelines may be desired and the authorities may consider this recommendation, that is upto them (Table 1).

Exemption of fees

There is a significant increase in fees (See Sixth Schedule), however for all molecules developed with financial support of the central or state government, fees are exempt. This eases burden on Universities and Institutes involved in drug development, if they are Central or State government grantees.

Post Trial Access

The Declaration of Helsinki provided for access to the investigational drug even after he trial to those subjects who have found it beneficial.[10] Since this is a guideline, subjects in India could not demand or claim post trial access unless the sponsor agreed to it. The NDCTR has however made post trial access a requirement, if the investigator recommends it and this is approved by the ethics committee. The Rule 27 puts certain conditions, namely the drug is for a condition for which there is no alternate therapy and the subject or legal heir has consented to the condition that the sponsor shall not be liable for post trial use. Meaning thereby, that should the subject suffer any AE or SAE, the sponsor shall not be required to pay for the medical treatment or compensation for the same.

New Problems

While the New Drugs and Clinical Trials Rules have been an advancement over the earlier Schedule Y, it has either created more problems, through vague or faulty drafting. This has led to problems that prevent the overall progress that the new rules would have brought about.

Conflict of Rule Numbers

The Drugs and Cosmetics Rules 1945 consisted of 169 Rules, numbered 1 to 169. The NDCTR contains 107 rules numbered 1 to 107. Thus, there is a duplication of 107 rules. To give an example Rule 96 of DCR is about Manner of Labelling, whileRule 96 of the NDCTR is Licence to manufacture an unapproved new drug but under clinical trial, for treatment of patient of life-threatening disease under the Drugs and Cosmetics Rules, 1945.

Thus, while mentioning or quoting any rules one would have to specify whether the rule number referred to the D and C rules or the NDCT Rules.

Are ECs mandatory?

Can an institute or organization desirous of conducting clinical trials get an approval from another organization, if it does not have its own EC? This question is rather difficult to answer.

Rule 6 says that whoever intends to conduct a clinical trial, or a BA/BE study must do so after an EC approval and that the EC should be registered. Rule 25 (i) clarifies that:

"clinical trial at each site shall be initiated after approval of the clinical trial protocol and other related documents by the Ethics Committee of that site, registered with the Central Licencing Authority under rule 8;"

It thus appears that for each site, the need for its own EC is absolute. But this is contradicted immediately in Rule 25 (ii) which states:

'where a clinical trial site does not have its own Ethics Committee, clinical trial at that site may be initiated after obtaining approval of the protocol from the Ethics Committee of another trial site; or an independent Ethics Committee for clinical trial constituted in accordance with

the provisions of rule 7"

It may further be pointed out that Institutional and Independent ECs are a thing of the past, the NDCTR does not recognize any Independent EC, one therefore wonders how it appeared in Rule 25 (ii). Secondly, Rule 7 is only about the composition of the EC for CT, BA and BE and not about independent ethics committees.

The same problems exist about the EC for Biomedical and Health Research, but since the entire chapter relating to this EC (Chapter IV) has been held in abeyance, no further comment on the same is warranted.

Composition of the EC

The Indian Council for Medical Research has provided a detailed and clear guideline for the composition of the Ethics Committee.[11] The EC for Biomedical and Health Research is required to have a composition as per the ICMR guideline (See Rule 15). However, when it comes to the composition of the EC for Clinical Trials, BA and BE studies, the composition recommended is different. (See Rule 7(1)). The description is incomplete and vague and raises more questions than it answers, such as

1. The mention of a lady member, raises the doubt that if the clinician is a lady, can she be counted as a lady or only as a clinician? (The question being whether one EC member can wear two hats at one time?)

2. The need for the pharmacologist appears not in the composition but in the quorum, where the qualifications of the pharmacologist are not clarified. The ICMR guideline is quite clear about the same.

It is clear that a single EC can be registered both for Clinical trials, BA and BE as well as for biomedical and health research, albeit with two registrations. Rule 16 (5) states so in no uncertain terms-

"Institutions desirous of conducting biomedical and health research as well as clinical trials or bioavailability or bioequivalence study shall require obtaining registration from specified authorities as provided in rule 8 and rule 17."

If a single committee is allowed to review and approve both types of research, in what way does a different composition help?

Powers of an EC

In the past the EC had powers to approve, require modifications or reject a research proposal. Once the Institute's EC rejected or disapproved a proposal, the only remedy for the investigator was an appeal for reconsideration. The EC could subsequently approve the proposal if the investigator provided adequate grounds to do so. The NDCTR has provided an additional mechanism of relief to such an aggrieved investigator. Rule 25 (iii) states as follows:

"In case an ethics committee of a clinical trial site rejects the approval of the protocol, the details of the same shall be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the clinical trial at the same site;"

An investigator could find another EC that would approve of the proposal and he/she could conduct the study at the institute whose EC had rejected the proposal. Further the investigator is required to submit the details of the EC decision to the CLA before approaching another EC. The rule does not say that the approval of the CLA is necessary. The problem with this rule is that it actually encourages EC shopping. One wonders why the new rules have brought in such a clause and how will this aid ethical research in the country?.

This rule (Rule 25(iii)) gives an upper hand to an outside EC, which would now provide oversight to the study. Rule 25(ii) does allow an investigator to approach another EC, but only if his/her parent institute did not have a registered EC. With the sub rule (iii) the investigator can go another EC even when the EC of the parent institute has rejected the study proposal.

Compensation

Compensation for clinical trial injuries is an important aspect of subject protection. As it is, due to different rules across the globe, there is lot of discrepancy among

Table 1: Timelines for receiving response from the regulators.

S. No	Activity	Current Timeline	Desired Timeline
1	Registration of an EC	45 days	--
1.1	Appeal in case of refusal	60 days	30 days
1.2	Decision on appeal	60 days	30 days
1.4	Re registration	45 days	--
2	Permission to conduct Clinical Trial (drug developed in India)	30 days*	--
3	Permission to conduct Clinical Trial (drug developed outside)	90 days	--
4	Permission to conduct BA/ BE Study	90 days	--

*If no permission/objection is received within the stipulated period, then it may be assumed that the regulator has no objection to conducting the study.

subjects of international studies.[12] There have been complaints that rules for compensation for clinical trial injuries are complicated,[13] there have been proposals for a simple compensation formula even in the US, where no compensation is provided by country's law.[14]

Nominee and legal heir are two distinct parties. The Legal Dictionary defines a nominee as "a person or entity who is requested or named to act for another, such as an agent or trustee." An heir is defined as "an individual appointed by law to succeed to the estate of an ancestor who died without a will. The term legal heir is commonly used to refer to a person who succeeds to property, either by will or law."

According to law, a nominee is a trustee and not the owner of the assets. In other words, he is only a caretaker of the assets. The nominee will only hold the assets (in this case the compensation) as a trustee and will be legally bound to transfer it to the legal heirs. For most investments, a legal heir is entitled to the assets of the deceased. Thus, anyone may appoint a nominee, but an heir can be decided by a will or by law. The two terms nominee and legal heir are not interchangeable, but the NDCTR has used them in this sense.

On the death of a participant, the compensation is required to be paid by the sponsor to the legal heir (Chapter VI, Rule 39(1)). The mechanism by which the sponsor or the investigator would identify the legal heir of the participant is not clear. In the ICF the participant has to declare the name of the nominee and their relation (Table 3, Third Schedule, NDCTR).

There appears little clarity on how the legal heirs are to be identified and whether it is the responsibility of the investigator to identify the legal heirs of deceased participants. In the past compensation was payable to the nominee, whose name was provided by the participant in the ICF. The legal heirs could lay their claim before the nominee and get their share without involving the sponsor or the investigator. The present rules put the onus on the sponsor for ensuring that the payment is made to the legal heirs.

The confusion between heir and nominee is likely to get the site and the sponsor involved in legal squabbles, for no fault of theirs. The government would do well to expeditiously amend the rule and revert to making compensation payable to the nominee as before. A simple and effective compensation rule is essential for ethical clinical research and any complication in this is likely to affect the quality clinical research in the country.[15]

Post Marketing studies

The rules lay down the requirements for post marketing studies of which three types are described in the Fifth Schedule. These include:

(A) Phase IV (Post marketing) trial

(B) Post marketing surveillance study

(C) Post marketing surveillance through periodic safety update reports

The schedule specifies that post marketing studies are to be done as per rule 77 and 82. Rule 77 deals with drugs imported for the purpose of sales and marketing while Rule 82 refers to drug manufactured for sales and marketing. Both these rules use the same language in subrule (iv), thus 77 (iv) and 82(iv) both state.

"As post marketing surveillance, the applicant shall submit Periodic Safety Update Reports as specified in the Fifth Schedule;"

The need for PSUR becomes clear, but when is the manufacturer supposed to do the Phase IV trial or the Post Marketing Study is not clear. Clarification on these issues will be helpful for sponsors, investigators and EC members.

CONCLUSION

Rules often follow the dictum one step forward and two back. In drug rules the situation is still favourable, they do take two steps forward, but one step back. New rules lead to many improvements, but they always come with some undesirable sections which offset a part of the advantages. The New Drugs and Clinical Trial Rules 2019, notified on 19th March 2019, that replace Part XA and Schedule Y of the Drugs and Cosmetics rules, do this. The draft rules were published on 1 February 2018 and over an year was given for comments and suggestions. The authors of this paper are unaware how many suggestions were received by the CDSCO, however the Ethical Research Initiatives, a Pune based non-profit organization for the promotion of research ethics had sent a 13 page a document with 23 suggested changes. Of these only one change has been incorporated and this referred to the pre-payment of 60% of compensation by the sponsor within 30 days, which would be non-refundable. In this paper we have highlighted the inconsistencies and sections which are likely to damage clinical research in the country. We bring the drawbacks in the NDCTR so that there is a nationwide understanding of the drawbacks of the rules. We also request the authorities to consider these problems

and issue amendments as early as possible.

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None.

CONFLICT OF INTEREST

None.

ABBREVIATIONS

AE: Adverse Event; **BA:** Bioavailability; **BE:** Bioequivalence; **CDSCO:** Central Drugs Standard Control Organisation; **CLA:** Central Licensing Authority; **CT:** Clinical Trial; **DCR:** Drugs and Cosmetics Rule, 1945; **DCGI:** Drugs Controller General, India; **EC:** Ethics Committee; **FDA:** Food and Drug Administration; **ICF:** Informed Consent Form; **ICH:** International Conference for Harmonisation; **ICMR:** Indian Council of Medical Research; **NDCTR:** New Drugs Clinical Trial Regulations; **PSUR:** Periodic Safety Update Reports; **SAE:** Serious Adverse Event; **TRIPS:** Trade Related Aspects of Intellectual Property Rights.

SUMMARY

The Government has notified the New Drugs and Clinical Trial Rules in March 2019. These rules have clarified a number of issues and brought about improvement in existing rules. Notable among these is the introduction of timelines for many permissions and clearances. Many advantages that accrue from these rules may be offset by certain inconsistencies that have crept in. It is requested that the authorities amend the rules, since they may cause problems for the conduct of clinical trials.

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