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Review Article

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Comparative Analysis of New Drugs and Clinical Trial Rules 2019 and its impact on Approval process of Oncology Drugs

Shagun Sharma*[,a], Khushbu Sharma[b], Pooja Verma[b], Shivali Rahi[a], Arpana Rana[a]

[a]*Advanced Institute of Pharmacy, Palwal, Haryana, India -121102*
[b]*H.R. Institute of Pharmacy, Ghaziabad, Uttar Pradesh 201003*

Abstract

With the aim to make India as the hub for Clinical Trials and promote a transparent and faster drug approvals process for the early availability and accessibility of drugs in the country the New Drugs and Clinical Trials Rules were published on March 19, 2019. The subsequent amendments were also proposed from time to time from March 2019 till June 2022 to make the regulations and the processes more robust.

The 'New CT Rules' replaced the Part XA and Schedule Y of the Drugs and Cosmetics Rules 1945. The NDCT rules will be applicable to all Investigational New Drugs, Biologicals, New Drugs, and Subsequent New Drugs. These rules also laid down the procedures for the effective working of Ethics Committees. The 'New Rules' comes up with many desirable changes that will bring transparency, predictability and well defined requirements to speed up the drug approval process in India. The New CT Rules provides a defined protocol so that decision making becomes uniform and that mainly focuses on the Quality & Safety of Clinical Trials. With these rules in place the regulatory system aims to make India a global clinical hub, approvals for the drugs with predictable, transparent and effective regulations and to make faster availability of new drugs to Indian population. In this article, we have highlighted the key developments/changes in the revised regulatory pathway for clinical trials in India and brought the comparative analysis of what has changed from the previous rules till date as subsequent amendments were also notified from time to time. Also, the present work aims at providing the impact of NDCT rules 2019 and subsequent amendments on approval process of drugs for life threatening diseases, unmet medical need and rare Diseases like Cancer.

By these rules in place Indian pharmaceutical industry would be able to bring a number of medicines which could be promising and effective in treating this pandemic for which no country in the world has been able to find any cure so far. The clause for local CT waiver, accelerated approval, reduced times for CT application is like a boon for developing new drugs in India. This will ensure faster availability of drugs in the country for life threatening diseases, unmet medical needs and rare disease like Cancer. Thus, proving it right that NDCT rules and subsequent amendments brought to the rules will be developing the country's reputation across the globe and will harmonize the regulations in line with the International standards.

Keywords: NDCT Rules 2019, CT Waiver, Orphan Drugs, Unmet medical need, Deemed approval, Clinical Trial, CTRI

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*Corresponding author

1. Introduction

According to the Drugs and Cosmetics Act 1945 a "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, clinical or; pharmacological including pharmacodynamics, pharmacokinetics or; adverse effects, with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug. (1) It is a systematic study used to generate data to establish the safety and efficacy of the new drugs and investigational new drugs on the human subjects. Clinical trial studies define the pharmacological profile of the drug including pharmacodynamic/ pharmacokinetic or adverse effects before its introduction in the market for human use. Before testing the drugs on human subjects the drugs are first tested in animals (rodent and non-rodent species) to establish the safety and efficacy.

Changes in lifestyle, polluted environment, unhealthy living, stress and certain other factors are responsible for the emergence of various health disorders that may have impacted the public health. Due to these factors the discovery of new molecules for treating all such disorders becomes a vital move. Also, as the complex and the life threatening diseases are evolving specifically like cancer, we need advanced technologies and evolving treatments. For life threatening diseases approval process should also be expedited and for unmet medical needs the advanced therapies and treatment should available at a faster pace for the much needed patients. So, for unmet medical needs and life threatening diseases like Cancer, NDCT rule is a welcome step which laid down the provisions of Pre-submission meetings, expedited pathways, clinical trial waiver, criteria's for early accessibility and availability of the drug in the country.

Conducting of clinical trials ensures that the patients will have access to better medicines in the near future with better patient compliance, least side effects and improved therapeutic results especially for those therapies which are left out or do not have promising treatment available in the country. It is one of the robust ways to evaluate the clinical & preclinical data like whether the molecule would be safe and effective for human use. It takes around 10-12 years of intense studies on the molecule before its commercialization. In the recent years, India has become an attractive destination for conducting clinical trials because it offers rapid completion and reduced cost to the sponsors from Canada, Europe and US. Also, we meet the international requirements to conduct clinical trials and made India ready to participate in more global trials.

Cancer is one of the such diseases where promising treatments are not available in the country and new innovative trial designs like Basket trials, conditional approval based on the Phase II data and in certain cases with surrogate end points are being given by the Regulatory agencies internationally. NDCT rule brings provisions of expedited approvals, surrogate end points in line with the International standards for early availability of drugs for life threatening diseases and unmet medical needs. NDCT rules also bring in the definition of orphan drugs for the first time.

Clinical trials involve a group of participants on which these studies are carried out. However, it is mandatory to ensure the safety of the participants that no unethical practice is being followed with the subjects involved in these studies. So it is absolutely essential to follow the Ethical practices and the guidelines on Good clinical practices. However, before subjecting the group of people in the clinical studies it is necessary to take their consent on the same.

In 2012, a massive crackdown happened wherein the patients being part of the clinical trials were not educated about the possible risk associated with the trials and trials were conducted without taking informed consent from them. (2) It turned out to be entire direly different side of unethical practices behind the name of clinical trials. The compensations, the quantum of compensation and the formula to calculate the compensation for injuries, SAEs, deaths was not clearly defined.

However, there were numerous issues which needed to be addressed and required special focus to improve the overall standard of clinical trials in India.

- Many of the subjects involved in the trial belong to the lower income group. The uneducated and financially backward population are selected by Clinical Research Organizations (CROs) and exploited for their ignorance, moreover the only reward they get out of it is little financial aid.
- In many cases, informed consent is not taken and the possible risks associated with the trials are not communicated to them.
- Amendments of the Drugs and Cosmetics Act in 2013 addresses the concern of better protection to the vulnerable group. However, there were issues with regard to unclear language.
- The role of ethics committee was very limited. Ethics committee in many of the trials were not existing and if existing, people were not trained enough to understand the complexity of clinical trials.
- All the clinical trials were not registered on Clinical Trial Registry of India (CTRI), transparency was a big concern, Trials with negative results were not registered on the CTRI and a lot of unethical practices being followed in the conduct of these trials.
- Drug Approval process was three step process (SEC, Technical and Apex Committee) which was leading to delay in approvals.
- Clinical trial standards were not in line with the International standards.
- Regulatory system was not that robust and full proof to address the concerns of Ethical considerations in the clinical trial.

As the year, 2012 faced the worst scenario of clinical trials in India. However, the government vide an amendment G.S.R. 53(E) dated 30.01.2013 tightened the CT regulations. Consequently, the pharma companies started conducting trials outside the India. This led to the major decline in the sum of conducting clinical trials in India. In the wake of this Indian drug regulator amended the rules and regulations pertaining to clinical trials and addressed all the concerns to curb all the unethical practices being followed and make India a hub for Global Clinical trials. NDCT rules 2019 and subsequent amendments published from time to time address all these concerns and the new regulations cover the major aspects for promoting clinical research as well as clearly make the regulations more robust and is a welcome move for the Industry. The reduced timelines, Expedited approval pathways for the drugs for life threatening diseases, unmet medical need and rare diseases like Cancer, Clinical trial waiver criteria, post-trial access put India on the global map and regulations are in line with

International standards. Further, the concept of pre and post submission meetings is in line with USFDA pre-IND and pre-NDA meetings.

2. History of clinical trial rules in India

Clinical trial in relation to a new drug or investigational new drug means any systematic study of a new drug or investigational new drug in human subjects to generate data for discovering or verifying its clinical or pharmacological parameters including pharmaco-dynamics, pharmacokinetics or adverse effects, with the objectives of determining the safety, efficacy or tolerance of such new drug or investigational new drug. They are the essential way that analysts discover out in case a new treatment, like a new drug, medical devices (for case, a pacemaker) is secure and viable in individuals. Clinical trials undergo through four developmental stages to test a treatment, discover the appropriate measurement, and explore side effects.

Phase 0 - Micro dosing study

Studies are done in small sample size. The purpose of this Phase is to help speed up & streamline the drug approval process. Phase 0 studies use few small doses of a new drug. The requirement if this phase is not available in India.

Phase 1 – Preliminary study

- Estimation of safety & tolerability
- No therapeutic objective.
- May involve one or combination objective such as MTD/PK/PD
- Preferably by trained investigator in clinical pharmacology.
- Healthy subject or in certain type of patients (where drug with potential toxicity) for case of anticancer drugs.
- First administration of IND into human subject.
- Small subject population.
- For new drug substance discovered in India clinical trial is required to be conducted right form phase 1

Phase 2 – Exploratory study

- To evaluate effectiveness of a drug for particular indication.
- To determine short term side effects & risk associated with drug.
- To determine dose & regimen for further studies in phase 2.

Phase 3- Confirmatory study

- Demonstration or confirmation of therapeutic benefits.
- To confirm that drug is safe & effective for use.
- To provided basis for marketing approval.
- Also, explore dose response relationship, use of drug in wider population, in different stages of disease or in combination with another drug.
- For new drugs approved outside India, phase 3 studies need to be carried out to generate evidence of efficacy & safety of drug in Indian patients when used as recommended in the prescribing information.

Phase 4-Post marketing study

- Phase 4 trial after the approval of the drug & related to the approved indication.
- May not be required at the time of drug approval.
- Phase 4 trials may include additional drug to drug interaction, dose response or safety studies & trial design to support use under the approved indication e.g. mortality or morbidity studies, epidemiological studies etc.
- It is in much wider population & go beyond safety & efficacy.

Post marketing assessment of new drug

Post marketing assessment (V schedule) of new drug may be carried out, in different ways, as under:

- Phase 4 (post marketing) trial.
- Post marketing study (PMS) or observational or non-interventional study for active surveillance.
- Post marketing surveillance through periodic safety update reports (PSUR).

Further, the concept of Basket trials, trials based on the surrogate end points and Real World evidence (RWE) data are some of the important consideration in the approval of a drug for life threatening diseases, unmet medical need and rare diseases like cancer.

Clinical trials were earlier conducted in accordance with the requirements set out in Schedule Y of the Drugs and Cosmetics Rules, 1945 (D&C Rules). However, there were many concerns regarding patient safety and compensation, approval timelines, and ethical consideration, etc. When unscrupulous activities were callously carried out in 2012, the matter was considered and regulatory aspects of clinical trials were discussed by the Regulatory Authority. So, to overcome such malpractices, certain amendments were made to the D&C Rules in 2013 to regulate such trials conducted in India. Accordingly, Rule-122DAB was inserted for providing compensation to an affected clinical trial subject in case of injury or death during a clinical trial. However, later vide the Drugs and Cosmetics (Second Amendment) Rules, Rule-122DAC was inserted into the D&C Rules, 2014, which lists out the conditions for the conduct of clinical trials which included, inter alia, the requirement to comply with Schedule Y of the D&C Rules, getting approval of an Ethics Committee, registration of the trials with the CTRI (Clinical Trials Registry of India), submission SAE reports. (3)

The restricted clinical trial regulations in the form of Amendments resulted in the reduced number of clinical trial conducted in India by pharmaceutical companies. The US National Institutes of Health (NIH) confirmed about post-pone of 30 clinical trials and likewise stopped enrolling participants in some more trials in India after the announcement of the new clinical trials rule in 2013. The unexpected drop in clinical research in India, compelled the government to fragment some of these rules in 2015. Consequently, to overcome the challenge of reduced clinical research in India, CDSCO revisited the rules on clinical trials and new drugs and introduced New Drugs and Clinical Trials Rules, 2019 and subsequent amendments thereof. (4)

3. Key Features of New Clinical Trial Rules 2019

NDCT rules are divided into the below mentioned chapters:

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

There are eight schedules each dealing with a particular heading, making searching of information very easy. (1,5,6)

3.1 Key Highlights of New Drugs and CT Rules (1, 3-10)

a. Introduction to the definition of Orphan Drugs- In the New Drug and Clinical Trial Rules, the definition of Orphan Drugs is very clearly elaborated however in the previous rules there was no clarity for the said definition. The new rules defined the orphan drugs as "drug intended to treat a condition which affects not more than 5 lakh persons in India." Additionally, in the new rules Phase III and Phase IV studies are exempted for orphan drugs. No application fee will be charged to develop Orphan Drugs assisting it with expeditious review process in line with the International standards. This will incentivize the Pharma companies to invest in research and development of Orphan drugs. Further, In case of cancer, most of the cancers are rare in nature, so in life threatening rare disease there is a strong need for the expedited pathway and waiver of Phase III/Phase IV trial. NDCT rules brings such provisions of CT waivers and Expedited approvals for rare diseases like rare cancers.

b. Ethics Committee- The new rules introduced two types of ECs, one for Clinical Trials, BA and BE studies and other for Biomedical and Health Research. (7) The current rules emphasize the role of EC to supervise the drug developments during clinical trials which was earlier only limited for scrutiny and approval of only BA/BE studies wherein its responsibility was to check whether the test drugs are acting in the similar direction to that of innovator or the reference drug. On the other side EC responsible for Biomedical and Health Research, will play an active role in monitoring the institutional clinical trials. In the previous rules, the regulations of Drug and Cosmetic Rules regarding Ethics Committee was only limited to CT, BA/BE studies. Any other studies apart from these had insufficient regulatory control over it. Consequently, became a pool of vast unethical practices of researchers and the university ethics committees. Earlier these studies were covered under ICMR guidelines on National Ethical guidelines for Biomedical and Health research which do not clearly define the approval mechanism and compensation process. However, the new rules mandates that the ethics committee shall be registered with the Department of Health Research (DHR) to overlook the institutional clinical trials as well.

c. Reduced Timelines/Deemed approval- This is one of the most welcoming step that encourages early access to the drugs. The approval timelines for domestic trial and global clinical trials has come down to 30 and 90 days respectively. In case if the applicant does not receive any communication during this period, the permission to conduct the clinical trial shall be deemed to have been granted by the Central Licensing Authority 1, 8. This is one of the most important and welcome step bringing more predictability for the approval timelines. Reduced timelines become even more important for cancer drugs as this will ensure quicker approval of cancer drugs for unmet medical need.

d. Compensation for injuries and death- This is regarded as one of the most important changes brought in the New Clinical Trial Rules. There have been numerous instances where the trial subjects who faced injuries and death in certain cases were not given enough compensation to the nominee or legal heir. In these rules, a separate Schedule is illustrated which only deals with compensation in case of injury or death in clinical trial or bioavailability or bioequivalence studies of new drugs or investigational new drugs. In Schedule VII of the New Clinical Trial Rules, the formula to determine the quantum of compensation in the cases of clinical trial related injury or death is specified. The clause become even more important for the cancer drugs. Though there is a strong need for the quicker availability of drugs but it's also very important to have all the ethical considerations in the conduct of clinical trial. Defining the quantum of compensation will make the regulatory process more robust and is a welcome move.

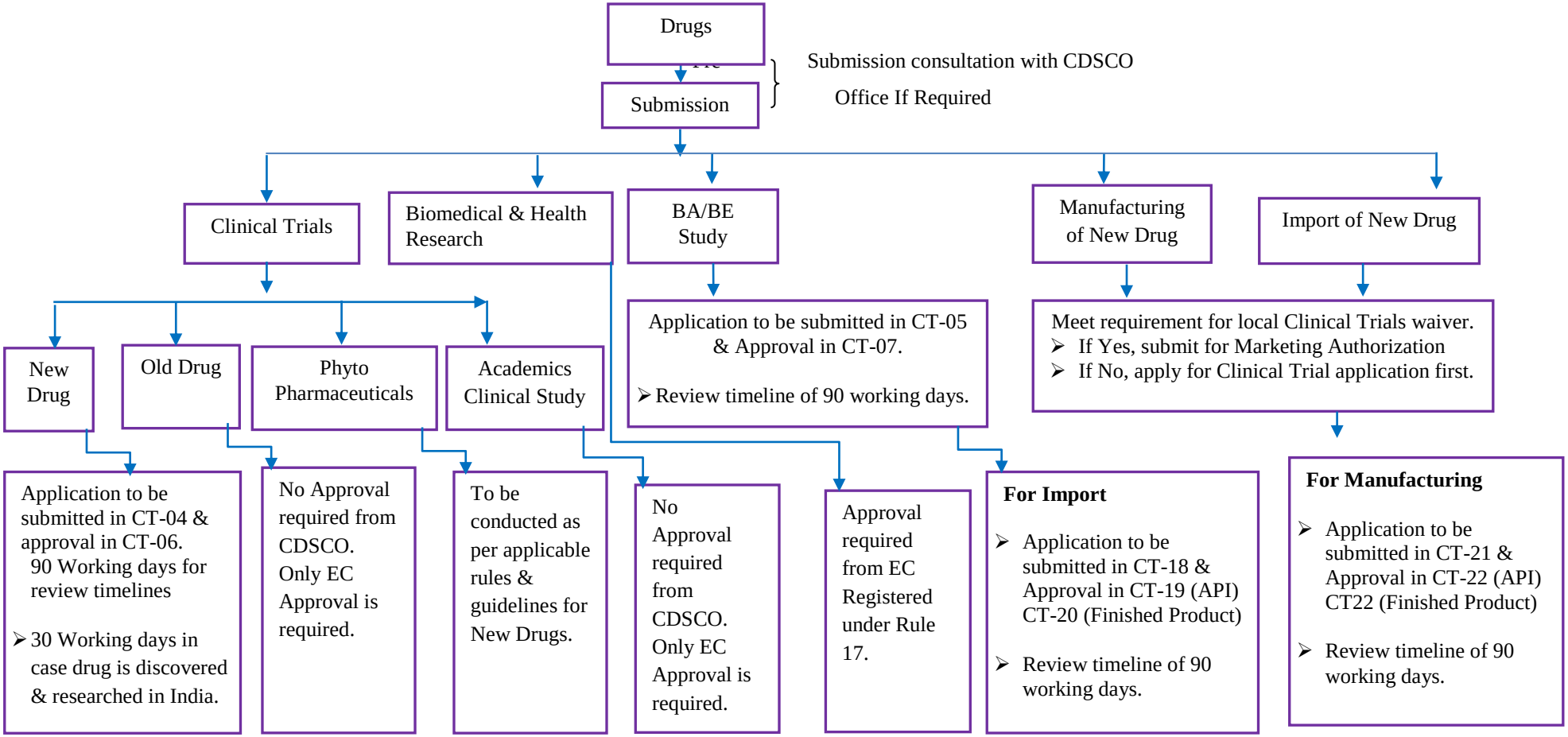

Figure 1. Regulatory Pathway for Product Registration

Table 1. Comparative table for New Drugs and Clinical Trial Rules 2019 and subsequent amendment thereof and impact assessment with previous rules (1,3-10)

S.No.	Key Features/Rules	New CT Rules	Former Rules	Impact Assessment
	CHAPTER I – PRELIMINARY			
1	**Definitions-** **New Definitions** **Modified Definition**	New definitions have been introduced for • Academic Clinical trial • Biomedical & Health Research • Clinical Trial Site • Efficacy • GCP guidelines • Orphan Drugs • Post trail Access • Registered Pharmacist • Similar Biologic • Trial Subject New Drug Definition has been modified to "a modified or sustained release form of a drug or novel drug delivery system of any drug approved by CLA"	These terms were not clearly defined in the former rules. MR/SR formulations were not regarded as a new drug after 4 years from the time of initial approval	More comprehensive definitions with better clarity.
	CHAPTER II – AUTHORITIES AND OFFICERS			
2	**Delegation of Powers of CLA**	The Drugs Controller, India, with the prior approval of the Central Government, may, by an order in writing, delegate all or any of powers of the Central Licencing Authority to any other officer of the CDSCO not below the rank of Assistant Drugs Controller (India). [Rule 4]	The licensing authority may with the approval of the Central Government by an order in writing delegate the power to sign licences and Registration Certificate and such other powers as may be specified in the order to any other person under his control. [Rule 22]	Step towards compliances and maintain the flow of work.
	CHAPTER III – ETHICS COMMITTEE FOR CT BA/BE STUDIES			
3(a)	**Constitution of Ethics Committee and Training Requirements**	➢ Minimum 7 members from medical, non-medical, scientific and non-scientific areas including one lay person, one-woman member, one legal expert & one independent member from any other related field such as social scientist, theologian or ethicist. ➢ There should be at least 50% members from outside the institute/organization in which EC is constituted. ➢ Every member of the Ethics Committee shall be required to undergo such training and development programmes as may be specified by the CLA from time to time. Provided that any member, who has not successfully completed such training and developmental programmes, shall be disqualified to hold the post of member of the Ethics Committee and shall cease to be a member of such committee.	There should be appropriate gender representation on the Ethics Committee. No such requirements previously. Members should be conversant with the provisions of clinical trials under this Schedule, Good Clinical Practice Guidelines for clinical trials in India and other regulatory requirements to safeguard the rights, safety and well-being of the trial subjects.	Several ECs may have to be re-constituted to comply to the rules Unethical practices followed earlier can be avoided. EC members will be having updated knowledge of the latest changes in the regulations. This will further enhance the knowledge standard of the committee members.
3(b)	**Registration of EC & Approval timelines**	Application to CLA shall be made in Form CT-01 45 working days from the date of receipt of application. Applicant may appeal within 60 working days. Central Govt shall dispose of	No specific provision was defined earlier. 100 days approval time considered as per DCGI office order dated 30 May 2014. No defined process for making appeal to	Reduces timelines will help in getting approval faster. Applicant can raise their point if they

		the appeal within 60 working days	Central Government in case applicant is not satisfied with CLA decision. Applicant could appeal to Central Government in case the EC registration is cancelled or suspended, within 90 days or receipt of the order of CLA.	believe any erroneous decision is taken by the Authority.
3(c)	**Validity of Registration**	Increased to 5 years. Renewal application shall be submitted 90 days prior to the expiry of registration	3 years. Renewal application shall be submitted 90 days prior to the expiry of registration	Lesser complex process for renewal of EC. This will certainly allow EC to be functional for longer period of time.
3(d)	**Proceedings of EC for clinical trial**	Any change in the constitution/membership of the registered EC shall be intimated to CLA within 30 working days	The Licensing Authority shall be informed in writing in case of any change in the membership or the constitution of the Ethics Committee takes place	One of the important steps for Maintaining Compliance
3(e)	**Maintenance of Records**	The Ethics Committee shall maintain data, record, registers and other documents related to the functioning and review of CT or BA/BE study, as the case may be, **for a period of five years** after completion of such clinical trial. Additional records to be maintained by EC: • recommendation given by EC for determination of compensation; • records relating to the serious adverse event, medical management of trial subjects and compensation paid	All records shall be safely maintained after the completion or termination of the study **for not less than five years** from the date of completion or termination of the trial (Both in hard and soft copies). These records were not explicitly mentioned in the documents list to be maintained by EC	ECs must have to go through trainings and revise their SOPs.
	CHAPTER IV – ETHICS COMMITTEE FOR BIOMEDICAL AND HEALTH RESEARCH			
4.	**Ethics Committee for Biomedical & Health Research**	Introduction of specific rules for ECs pertaining to biomedical research. Any institution or organization which intends to conduct biomedical and health research shall be required to have an Ethics Committee to review and oversee the conduct of such research as detailed in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. Such EC shall be required to register with the authority designated by the Central Government in the Ministry of Health and Family Welfare, Department of Health Research	Such studies were also approved by the Ethics Committees registered with DCGI office under Rule 122DD	Impact on academic institutions to revamp existing ECs. This will eases the workload and enhances efficiency of EC functioning..
	CHAPTER V – CLINICAL TRIAL, BIOAVAILABILITY & BIOEQUIVALENCE STUDY OF NEW DRUGS AND INVESTIGATIONAL NEW DRUGS			
		PART A - CLINICAL TRIAL		
5(a)	**Application for permission to conduct clinical trial of a new drug or investigational new drug as part of discovery, research and manufacture in India**	Application to be submitted in Form CT 04. Permission granted in Form CT 06 **Approval timeline**–90 working days for drugs developed outside India Approval timeline –30 working days indigenous development **Provision of deemed approval** –if CLA does not communicated to applicant in 30 working days, the application is deemed to be approved. Applicant can submit Form CT-4A to CLA, which will become legal form, on record and shall be called automatic approval of CLA	Application to be submitted in Form 44. Permission granted as approval letter, not in any specific format. **Approval timeline** –120 days as per DCGI office order dated 30 May 2014 No differentiation was given previously in this regard There was **no provision of deemed approval** earlier	Reduced timelines with deemed approval will certainly encourage new drug development in India. Faster approvals will ensure early availability of drugs for life threatening and unmet medical needs like cancer.
5(b)	**Approval of Ethics Committee**	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. Provided that	The trial site(s) may accept the approval granted to the protocol by the EC of another trial site or the approval granted by an	Opens access to several new clinical trial sites for conducting trials

		the approving EC for clinical trial shall be responsible for the study at the trial site.	independent ethics committee (constituted as per Appendix VIII), provided that the approving EC(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.	
5(c)	**Communications related to EC approval process**	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 The Central Licensing Authority shall be informed about the approval granted by the Ethics Committee within a period of fifteen working days of the grant of such approval	No such requirements previously	One of the important step for notification to CLA and maintaining compliance.
5(d)	**Status Reports**	Status of enrolment of the trial subjects shall be submitted to the Central Licensing Authority on quarterly basis or as appropriate as per the duration of treatment in accordance with the approved clinical trial protocol, whichever is earlier •six monthly status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Central Licensing Authority electronically in the SUGAM portal	Annual status report of clinical trial was required to be submitted	One of the important step for notification to CLA and maintaining compliance.
5(e)	**Validity of permission**	Permission in CT-06 or CT-4A will be valid for two years from the date of issue, unless extended by the CLA	No validity / expiry was defined	CT has to be initiated within 2 years of the issuance of the permission. This will ensure the initiation of studies within defined timeframe.
5(f)	**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 such requirement previously	If the legal heir has consented the use of the drug in writing there will be no liability for post-trial use of IND on ND on the sponsor
5(g)	**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	No such requirement previously	ICMR guidelines to be followed. This may increase the burden on ethical compliance for ECs.
		PART B - BA/BE STUDY		
5(h)	**Application and approval process**	Application to be submitted in CT-05. Approval to be granted in CT-07 Approval timeline –90 working days In case an Ethics Committee of a bioavailability or bioequivalence study centre rejects the approval of the protocol, the details of the same should be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the BA/BE study at the same site The Central Licensing Authority shall be informed about the approval granted by the registered Ethics Committee within a period of 15 working days of the grant of such approval	No specific format was prescribed. No such requirement previously No such requirement previously	One of the important step for notification to CLA and maintaining compliance.
5(g)	**Validity of permission**	The permission to conduct BA/BE study granted under rule 34 in Form CT-07 shall remain valid for a period of one year from the date of its issue, unless suspended or cancelled by the Central Licensing Authority.	No such requirement previously	BA/BE study must be initiated within 1 year of permission granted. This will ensure the initiation of studies within defined

		• In exceptional circumstances, where the Central Licensing Authority is satisfied about the necessity for an extension beyond one year, the said authority may, on the request of the applicant made in writing, extend the period of permission granted for a further period of one year. • Study shall be initiated by enrolling the first subject within a period of one year from the date of grant of permission, failing which prior permission from the Central Licensing Authority shall be required		timeframe.
	CHAPTER VI – COMPENSATION			
6	**Compensation in Death Case/ Injury Case**	Sponsor & Investigator to forward their reports on SAE/SAE Death case after due analysis to CLA, Head of Institution **within 14 days of the knowledge of occurrence of SAE death & within 14 days of the reporting of SAE in injury case.**	Sponsor & Investigator to forward their reports on SAE Death case after due analysis to Licensing Authority, Head of Institution **within 14 days of the occurrence of SAE death & within 14 days of the occurrence of SAE in injury case**	Changed from the 'day of occurrence' of SAE to 'knowledge of occurrence' of SAE. However, it is a more practical approach
		Ethics Committee to forward their reports on SAE Death case/SAE after due analysis along with their opinion on financial compensation to CLA, within **30 days of receiving the report of the SAE death/SAE from investigator**	Ethics Committee to forward their reports on SAE Death case/SAE after due analysis along with their opinion on financial compensation to Licensing Authority, within **30 days of occurrence of the serious adverse event of death or SAE injury.**	Changed from the '**occurrence of the serious adverse event** to '**receiving the report of the SAE**' of SAE. However, it is a more practical approach
		CLA may constitute expert committee to examine the case and provide their recommendations to CLA. The committee shall provide its recommendation within 60 days of receipt of the report of SAE Death CLA may constitute expert committee to examine the case and provide their recommendations to CLA. The committee shall provide its recommendation within 60 days of receipt of the report of SAE.	Expert committee to provide their recommendations to Licensing Authority within 105 days of occurrence of the adverse event. The Licensing Authority shall have the option to constitute an independent Expert Committee, wherever considered necessary, to examine such serious adverse events of injury, which will recommend to the Licensing Authority for arriving at the cause considered necessary, to examine such serious adverse events of injury, which will recommend to the Licensing Authority for arriving at the cause of the injury and also the quantum of compensation in case of clinical trial related injury.	Reduced timelines and an important step to ensure ethical considerations in the Clinical trials and maintain compliances.
		CLA to pass orders to sponsor within 90 days of receipt of report of the SAE/ SAE Death	CLA to pass orders to sponsor within 150 days of occurrence of SAE/SAE Death	Reduced timelines ensuring faster approvals
	CHAPTER VII – BIOAVAILABILITY AND BIOEQUIVALENCE STUDY CENTRE			
7(a)	**Approval timelines**	Registration of BA BE centers will be granted in CT-09 within 90 working days from the date of receipt of the application in CT-08	BA BE center approval was granted in 60 days from the time of receipt of joint inspection report [Reference DCGI office order dt 30 May 2014].	Reduced timelines ensuring faster approvals

7(b)	**Validity of registration**	Registration is valid for 5 years from date of issue	Approval is valid for 3 years	More streamlined and less cumbersome processes.
7(c)	**Renewal applications**	Renewal applications shall be submitted 90 days prior to expiry of registration	Application for renewal of approval shall be submitted 4 months before the expiry of present approval	No major impact.
7(d)	**Records Maintenance**	For a period of five years after completion of such study or for at least two years after the expiration date of the batch of the new drug or investigational new drug studied, whichever is later;	For at least 2 years after expiry of the batch	Important step for maintaining records, compliances and ethical considerations in the Clinical trials.
	CHAPTER VIII –MANUFACTURE OF NEW DRUGS OR IND FOR CT, BA, BE OR FOR EXAMINATION TEST AND ANALYSIS			
8(a)	**Approval process & Timeline**	Application to be submitted in CT-10. Approval to be granted in CT-11 Approval timeline –90 working days	No specific format prescribed for application or approval [Form 29 NOC] Approval timeline –60 days	This will lead to Reduced timelines and Faster approvals.
8(b)	**Approval validity**	The permission will remain valid for 3 years, Extension of 1 year may be granted	No validity defined for Form 29 NOC	This makes the process Less cumbersome.
8(c)	**Condition of License**	Manufacturing of drugs shall be in accordance with the principles of Good Manufacturing Practices;	This was not explicitly defined earlier.	Important step to ensure the quality of drug used in the CT and to follow the GMP principles.
	CHAPTER IX - IMPORT OF NEW DRUGS AND IND FOR CT, BA, BE OR FOR EXAMINATION TEST AND ANALYSIS			
9(a)	**Approval process & Timeline**	Application to be submitted in CT-16 Approval to be granted in CT-17 Approval timeline –90 days	Application submitted in Form 12 Approval granted in Form 11 Approval timeline –45 days	This will lead to Reduced timelines and Faster approvals.
9(b)	**Approval validity**	The licence will remain valid for 3 years, Extension of 1 year may be granted	3 years No provision of extension. New license may be obtained instead.	This makes the process Less cumbersome.
9(c)	**Condition of License**	Manufacturing of drugs shall be in accordance with the principles of Good Manufacturing Practices;	This was not explicitly defined earlier.	Important step to maintain Compliances.
	CHAPTER X – IMPORT OR MANUFACTURE OF NEW DRUGS FOR SALE OR FOR DISTRIBUTION			
10(a)	**Permission to import a new drug**	Application to be submitted in CT-18 Approval to be granted in CT-19 [API] or CT-20 [Finished formulation] Approval timeline –90 working days Conditions for waiver of local clinical trials are defined very clearly in the new regulations.	Application submitted in Form 44 Approval granted in Form 45 [Finished formulation] or Form 45A [API] Approval timeline –180 days Local clinical trials may not be necessary if the drug is of such a nature that the Licensing Authority may, in public interest, decide to grant such permission on the basis of data available from other countries	This will lead to Reduced timelines and Faster approvals. Waiver for the local CT is an important move for faster approval of drugs for life threatening diseases, unmet medical needs and rare diseases. Faster approvals and Clinical trial waiver will ensure early availability of drugs for life threatening diseases, unmet medical needs and rare disease like cancer.
10(b)	**Permission to manufacture a new drug**	Application to be submitted in CT-21 Approval to be granted in CT-22 [API] or CT-22 [Finished formulation] Approval timeline –90 working days Conditions for waiver of local clinical trials are defined very clearly in the new regulations.	Application submitted in Form 44 Approval granted in Form 46 [Finished formulation] or Form 46A [API] Approval timeline –180 days Local clinical trials may not be necessary if the drug is of such nature that the Licensing Authority in Rule 21 may, in public interest, decide to grant such permission on the basis	This will lead to Reduced timelines and Faster approvals. Waiver for the local CT is an important move for faster approval of drugs for life threatening diseases, unmet medical needs and rare diseases. Faster approvals and Clinical trial waiver will ensure early availability of drugs for

			of data available from other countries.	life threatening diseases, unmet medical needs and rare disease like cancer.
	CHAPTER XI - IMPORT OR MANUFACTURE OF UNAPPROVED NEW DRUG FOR TREATMENT OF PATIENTS IN GOVERNMENT HOSPITAL AND GOVERNMENT MEDICAL INSTITUTION			
11(a)	**Permission to import a new drug by a govt hospital and govt medical institution**	Application to be submitted in CT-24 Import License to be granted in CT-25 Approval timeline –90 working days Validity of license –3 years Half yearly report is to be submitted by the govt hospital or medical institution to CLA about status and stock of the unapproved drugs imported, utilized and destroyed	Application submitted in Form 12-AA Approval granted in Form 11-A Approval timeline –not defined Validity of license –1 year No requirement of submitting such report	Defined approval timelines. Less cumbersome process
11(b)	**Permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease**	Where any medical officer of a Government hospital or Government medical institution prescribes in special circumstances any new drug for a patient suffering from serious or life threatening disease for which there is no satisfactory therapy available in the country and which is not yet approved by the Central Licencing Authority but the same is under clinical trial in the country, then, such new drug may be approved to be manufactured in limited quantity subject to provisions of these rules. Application to be submitted in CT-26 Import License to be granted in CT-27 Approval timeline –90 days Validity of permission –1 year The permission holder shall inform the Central Licensing Authority of the occurrence of any serious adverse event and action taken thereon including any recall within fifteen days of occurrence of such event.	No such provision was available earlier	This is a welcome move that will provide the necessary treatment to the patients who suffered due to unavailability of the effective therapy. The step becomes more important and relevant for drugs for rare diseases, life threatening and unmet medical needs like cancer.
	CHAPTER XIII – MISCELLANEOUS			
13(a)	**Pre Submission Meeting**	Provisions included for pre-submission meeting. In the pre submission meeting, Application, with fee accompanied by particulars and documents to be submitted, the DCGI or any other authorized person, shall provide suitable clarification to the applicant. Central Licencing Authority shall, within a period of thirty days, intimate the facts to the applicant in writing and direct him to furnish such further information or documents as necessary.	Not applicable. Pre-submission meeting is a new concept	One of the important step in line with the International Regulatory agencies to get the guidance from the Indian HA on the clinical study design and other critical considerations for the faster availability of drug. The step becomes more important and relevant for drugs for rare diseases, life threatening and unmet medical needs like cancer.
13(b)	**Post Submission Meeting**	If the applicant desires to seek clarification in person in respect of pending application and queries related thereto, the applicant may make an application for a post-submission meeting with the officer designated by the Central Licensing Authority within a period of fifteen days from the date the query was received for seeking guidance with regards to the queries concerning pending application. The applicant shall clearly state the points on which clarification is required and after receipt of such application, the designated officer shall inform the time and date scheduled for post submission meeting. In the post submission meeting, the officer designated by the Central	Not applicable. Post-submission meeting is a new concept	One of the important step in line with the International Regulatory agencies to get the guidance from the Indian HA for the faster availability of drug. The step becomes more important and relevant for drugs for rare diseases, life threatening and unmet medical needs like cancer.

		Licensing Authority shall provide suitable clarification to the applicant. The summary of the clarification provided by the designated officer shall be made available to the applicant.		
	SCHEDULE I - General Principles and Practices for Clinical Trial			
	No changes			
	SCHEDULE II - Requirements and guidelines for permission to import or manufacture of new drug for sale or to undertake clinical Trial			
	Provision for Accelerated Approval Process	**Accelerated approval process** may be allowed to a new drug for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of alternative treatments, provided that there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment. a**)** In such case, the approval of the new drug may be based on data generated in clinical trial where surrogate endpoints rather than using standard outcome measures such as survival or disease progression, which are reasonably likely to predict clinical benefit, or a clinical endpoint. b**)** Post marketing trials will be required to validate the anticipated clinical benefit. c) Accelerated approval may also be granted to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease of special relevance to the country, and addresses unmet medical needs. d) If the remarkable efficacy is observed with a defined dose in the Phase II clinical trial of investigational new drug for the unmet medical needs of serious and life threatening diseases in the country, it may be considered for grant of marketing approval by the Central Licensing Authority based on Phase II clinical trial data. In such cases, additional post licensure studies may be required to be conducted after approval to generate the data on larger population to further verify and describe the clinical benefits	No specific provisions existed earlier	To be allowed to a new drug for a disease, depending on severity, rarity, or prevalence and the availability or lack of alternative treatment. The step becomes more important and relevant for drugs for rare diseases, life threatening and unmet medical needs like cancer.
	Provision for quick or expeditious review process for approval of a new drug after clinical development:	Situations where quick or expeditious review process can be sought for approval of a new drug after clinical development: a) In situation where the evidence for clinical safety and efficacy have been established even if the drug has not completed the all or normal clinical trial phases, the sponsor or applicant may apply to the licensing authority for expedited review process wherein the licensing authority will examine and satisfy the conditions as specified under clause 1 (2) (ii) (B) (i) of Second Schedule b) The sponsor or applicant may also apply to the licensing authority for expedited review process for new drugs developed for disaster or defense use in extraordinary situation, such as war time, the radiation exposure by accident or intention, sudden deployment of forces at areas with higher health risk, where specific preventive and treatment strategy is required, here new intervention in the form of new drug, route of delivery or formulation has been developed and were real life clinical trial may not be possible. The permission for manufacture of such new drug may be granted subject to conditions as specified under clause 1 (2) (ii) (B) (ii) of Second Schedule c) The new drug is an orphan drug as defined in clause (x) of rule 2 of these	No specific provisions existed earlier	Although, post marketing trials shall be required for clinical benefit. The step becomes more important and relevant for drugs for rare diseases, life threatening and unmet medical needs like cancer.

		Rules		
	Stability data requirements for new drug substances and formulations intended to be Stored under general conditions **Stored in a refrigerator** **Stored in a freezer**	Long term :30°C ±2°C/75% RH ±5% RH –6 or 12 months Accelerated: 40°C ±2°C/75% RH ±5% RH -6 months Long term: 5°C ±3°C –6 or 12 months Accelerated: 25°C ±2°C/60% RH ±5% RH -6 months Long term: 5°C ±3°C –6 or 12 months	Long term: 30°C ±2°C/65% RH ±5% RH -12 months;Accelerated: 40°C ±2°C/75% RH ±5% RH -6 months Long term: 5°C ±3°C -12 months Accelerated: 25°C ±2°C/60% RH ±5% RH -6 months Long term:5°C ±3°C 12 months	Harmonized as per ICH guidelines, Zone IVB Stability zone for India.
	SCHEDULE III - CONDUCT OF CLINICAL TRIAL			
	Table 7 – Investigator Brochure	A format of Investigator Brochure has been included in rules.	Format of IB was provided in Indian GCP [Appendix IV]	The format and content of the IB prescribed in the new Rules is pretty much similar to existing format as per Indian GCP
	Table 8 – Prescribing Information	A specific template has been provided for Prescribing Information under Table 8 of Third Schedule.	Content of Prescribing Information was prescribed under Clause 1 (1) (vi) of Schedule Y.	Information like 'Patient counselling information', 'Details of manufacturer', 'Details of permission or license number with date' are some additional requirements of PI document in the new rules.
	SCHEDULE IV- REQUIREMENTS AND GUIDELINES FOR CONDUCT OF BA BE STUDY OF NEW DRUGS OF INVESTIGATIONAL NEW DRUGS			
	Requirements and guidelines for conduct of BA BE study of new drugs of investigational new drugs	The requirements of BA BE studies are explicitly prescribed under Fourth Schedule of the Rules. Clearly defined process for; • General principles • BA BE study centre • Organisation and management • Documented SOPs • Clinical Pharmacological Unit • Maintenance of records • Retention of samples	Requirements were not very explicit in the Rule book.	More comprehensive requirements and processes with better clarity.
	SCHEDULE V- POST MARKET ASSESSMENT			
A.	**Phase IV [Post Marketing trial]**	Defined process & fees for approval of Phase IV studies have been provided in the new rules Phase IV study fees –INR 200,000	No fees was defined earlier for Phase IV studies	Distinction between Phase 4 trials and Post-Marketing Surveillance (PMS) studies. RWE is the new terminology adopted by many of International agencies and these studies become more important and relevant for drugs for rare diseases, life threatening and unmet medical needs like cancer.
B.	**Post marketing surveillance study**	Such studies will now need DCGI approval Inclusion or exclusion of subject are decided as per the recommended use as	Previously, Not clear whether Non interventional/Observational studies would	As post marketing surveillance, the applicant shall submit Periodic Safety

	or observational or non-interventional study for active surveillance	per prescribing information or approved package insert. In such studies the study drugs are the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable	also require approval from DCGI – still a grey area.	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. RWE is the new terminology adopted by many of International agencies and these studies become more important and relevant for drugs for rare diseases, life threatening and unmet medical needs like cancer
C.	**Post marketing surveillance through PSURs**	Format of PSUR is slightly changed and it is more elaborated now Information about Risk Management Plan is now part of PSUR document Copy of marketing authorization in India is to be enclosed with PSUR	The brief format of PSUR was prescribed in Schedule Y Information about Risk Management Plan was not required to be part of PSUR earlier Copy of marketing authorization in India was not required	PSURs submission mandatory–defined structure of PSUR content & structure, now aligned with EU PBRER (ICH) format which is very detailed and exhaustive. The timeline for submission to DCGI is still is retained as '30 calendar days',

SCHEDULE VI- FEE PAYABLE FOR LICENCE, PERMISSION AND REGISTRATION CERTIFICATE

S.No.	Type of application	Previous fees	New fees
1	Clinical trial – Phase I	50,000 INR	300,000 INR
2	Clinical trial – Phase II, III	25,000 INR	200,000 INR
3	Clinical trial – Phase IV	No fees	200,000 INR
4	Reconsideration of clinical trial application	No fees	50,000 INR
5	BA / BE study	25000 for drugs approved within 1 year & 15000 for drugs b/w 1 to 4 years	200,000 INR
6	Reconsideration of BA / BE study application	No fees	50,000 INR
7	Registration of BA BE centre	No fees	500,000 INR
8	Reconsideration of BA / BE centre application	No fees	100,000 INR
9	Permission to manufacture new drugs or investigational new drugs for clinical trial or BE BE Study	No fees	5000 INR per product
10	Reconsideration of application to manufacture new drugs or investigational new drugs for clinical trial or BA BE study	No fees	2000 INR per product
11	Import of new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis	5000 INR for first drug and 2000 INR for every additional drug	5000 INR per product
12	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	No fees	1000 INR
13	Permission to import new drug (Finished Formulation or API) for marketing	250,000 INR	500,000 INR
14	Permission to import new Drug (Finished Formulation or API) already approved in the country for marketing	100,000 INR	200,000 INR
15	Reconsideration of application for permission to import new drug for marketing	No fees	50,000 INR
16	Application for permission to import approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for marketing	100,000 INR	300,000 INR

17	Application for permission to import fixed dose combination having one or more of the ingredients as unapproved new molecules for Marketing	250,000 INR	500,000 INR
18	Application for permission to import fixed Dose combination having approved ingredients for marketing	100,000 INR	400,000 INR
19	Application for permission to import fixed dose combination already approved for Marketing	100,000 INR	200,000 INR
20	Application for permission to import fixed dose combination for new claims, new indication or new dosage form or new route of administration or new strength for marketing	100,000 INR	300,000 INR
21	Application for permission to manufacture new drug (Finished Formulation or Active Pharmaceutical Ingredient) for sale or Distribution	50,000 INR	500,000 INR
22	Application for permission to manufacture new drug (Finished formulation or Active Pharmaceutical Ingredient) already approved in the country for sale or distribution	50,000 INR or 15,000 INR	200,000 INR
23	Application for permission to manufacture approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for sale or distribution	15,000 INR	300,000 INR
24	Application for permission to manufacture fixed dose combination having one or more of the ingredients as unapproved new molecules for sale or distribution	50,000 INR	500,000 INR
25	Application for permission to manufacture fixed dose combination having approved ingredients for sale or distribution	15,000 INR	300,000 INR
26	Application for permission to manufacture fixed dose combination already approved for sale or distribution	15,000 INR	200,000 INR
27	Application for permission to manufacture fixed dose combination for new claims, new indication or new dosage form or new route of administration or new strength for sale or distribution	15,000 INR	300,000 INR
28	Reconsideration of application for permission to manufacture new drug for sale or distribution	No fees	50,000 INR
29	Application for Import of unapproved new drug by Government hospital and medical institution	600 INR for first drug, 300 INR for additional drugs	10,000 INR
30	Application for permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease	No provision	5,000 INR
31	Pre-submission meeting	No provision / fees	500,000 INR
32	Post submission meeting	No provision / fees	50,000 INR
33	Any other application	No provision / fees	50,000 INR

Revision in application fees for Cosmetics Registration after Revision in FEES vide GSR no. 1193 (E) dated 12th December, 2018

Note 1: No fee shall be chargeable in respect of application for conduct of clinical trial for orphan drugs.

Note 2: 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.

Type of application		**Previous fees**	**New fees**
34	Cosmetics Registration	$ 250 per Category	$ 2000 per Category

SCHEDULE VII - FORMULAE TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED INJURY OR DEATH

SCHEDULE VIII – FORMS PRESCRIBED UNDER NEW DRUGS AND CLINICAL TRIAL RULES

	Type of Application	**Rule(s)**	**New Form**	**Old Form**
1	Application for registration/renewal of Ethics Committee (EC) relating to CT or BA/BE study or Biomedical Health Research.	8, 10, 17	FORM CT-01	No specific format was prescribed
2	Grant of registration of EC relating to CT or BA/BE study.	8, 9, 10, 14	FORM CT-02	No specific format was prescribed
3	Grant of registration of EC relating to Biomedical Health Research.	17, 18	FORM CT-03	No specific format was prescribed
4	Application to conduct clinical trial of new drug or Investigational new drug.	21	FORM CT-04	Form 44
5	Information to initiate clinical trial of new drug or investigational new drug as part of discovery,	23	FORM CT-4A	No specific format was

	research and manufacture in India.			prescribed
6	Application to conduct BA/BE study.	33	FORM CT-05	No specific format was prescribed
7	Permission to conduct clinical trial of new drug or IND.	22, 25, 26, 29, 30	FORM CT-06	Permission granted in approval letter not in any specific format
8	Permission to conduct BA BE study of new drug or IND.	34, 35, 36, 37, 38	FORM CT-07	No specific format was prescribed
9	Application for registration/renewal of BA BE Centre.	45	FORM CT-08	No specific format was prescribed
10	Grant of registration of BA BE centre.	47, 48, 49, 50, 51	FORM CT-09	No specific format was prescribed
11	Application to manufacture new drug or IND for CT or BA/ BE study or for examination, test and analysis.	52	FORM CT-10	No specific format was prescribed
12	Permission to manufacture new drug or IND for CT or BA/BE study or for examination, test and Analysis.	53, 54, 55, 56, 57, 58	FORM CT-11	Form 29 NOC
13	Application to manufacture formulation of unapproved API for test or analysis or for CT or BA/BE study.	59	FORM CT-12	No specific format was prescribed
14	Application to manufacture unapproved API for development of formulation for test or analysis for CT or BA/BE study.	59, 60	FORM CT-13	No specific format was prescribed
15	Permission to manufacture formulation of unapproved active pharmaceutical Ingredient for test or analysis or for CT or BA BE study.	60, 61, 62, 63, 64	FORM CT-14	No specific format was prescribed
16	Permission to manufacture unapproved API for the development of formulation for test or analysis or CT or BA BE study.	60, 61, 62, 63,64	FORM CT-15	No specific format was prescribed
17	Application to import new drug or IND for CT or BA/BE for examination, test and analysis.	67	FORM CT-16	No specific format was prescribed
18	Licence to import new drug or IND for CT or BA/BE study or for examination, test and analysis.	68, 69, 70, 71, 72	FORM CT-17	No specific format was prescribed
19	Application to import new drug for sale or distribution.	75	FORM CT-18	Form 44
20	Permission to import new API for sale or distribution.	76, 77, 78	FORM CT-19	Form 45 A
21	Permission to import pharmaceutical formulations of new drug for sale or distribution.	76, 77, 78	FORM CT-20	Form 45
22	Application to manufacture new drug formulation for sale or distribution.	80	FORM CT-21	Form 44
23	Permission to manufacture new API for sale or distribution.	81, 82, 83, 84	FORM CT-22	Form 46
24	Permission to manufacture pharmaceutical formulation of new drug for sale or distribution.	81, 82, 83, 84	FORM CT-23	Form 46 A
25	Application for licence to import of unapproved new drug for treatment of Patients of life threatening disease in a government hospital or government Medical institution.	86	FORM CT-24	Form 12AA
26	Licence to import unapproved new drug for treatment of patients of life Threatening disease in a government hospital or medical institution.	87, 88, 89, 90	FORM CT-25	Form 11A
27	Application to manufacture unapproved new drug but under CT for treatment of patients of life threatening disease in a government hospital or medical institution.	91	FORM CT-26	No specific format was prescribed
28	Permission to manufacture unapproved new drug but under clinical trial for treatment of patients of life threatening disease in a government hospital or medical institution.	92, 93, 94, 95	FORM CT-27	No specific format was prescribed

e. Waivers for testing in India/ CT on drugs already approved outside India- As per Rule 75 of the New Drug & Clinical Trial Rules, there are specific conditions under which waiver for the local clinical trial requirement can be availed. (1,10)

- For drugs which are already approved and marketed by any regulated market of any country as specified by the DCGI with approval of government from time to time and certain other conditions may take waiver of the clinical trials.
- The waiver may be instituted if the drug is already approved for marketing in a country specified by the licensing authority and no major SAE have been reported, also meanwhile a global clinical trial is ongoing in India.
- Waiver can also be granted if there is an unmet medical need.
- It is also applicable for rare disease for which drugs are not available or available at a high cost or orphan drugs.

Clinical trial waiver criteria for orphan drugs and for unmet medical need will allow drugs for cancer and other rare diseases to come soon in India and will ensure the availability of these drugs in India. So defining the Clinical trial waiver criteria is one of the most important step to ensure the availability of drugs for unmet medical needs like cancer. Further, many of the cancers are rare in nature for which treatments are not available in the country. CT waiver criteria is one of the step of utmost importance to ensure approval and availability of drugs for rare cancers.

f. Provision for academic clinical trial: As per NDCT rules, clinical trials meant for Academic purposes may be conducted without the permission of CLA, but with the permission of Ethics committee. In case of uncertainty among the Academic clinical trials may add more value for proof of concept studies and for the evidence generation. Also, in case of incremental innovation academic trials may play a critical role.(1,9)

g. Provision for post-trial access- If the drug is found to be beneficial to the trial subject after completion of the trial and there is no alternative therapy available then the Investigator can recommend post-trial access for the patient without any cost. However, the trial subject or legal heir of the subject shall declare that in writing that the sponsor shall not be held liable for any adverse event for post-trial use of IND or ND.

h. Post Marketing Studies- The previous rules don't give the clear picture of the definition and requirements for Phase IV studies and Post Marketing Surveillance, however, the same has been rectified in the new rules. The NDCTR, 2019 specifies that, phase IV clinical trials study would come with studies related to; trials designed to support use under the approved indications drug-drug interactions, dose-response or safety studies and Post marketing studies are to be conducted in accordance with the approved indications and conditions of use with an objective of establishing safety as the primary end points and inclusion exclusion criteria as per approved package insert. In such studies, the study drugs included in the protocol are a part of the patient's treatment according to prescriber's directions.

4. Subsequent Amendments in NDCTR, 2019 to till date

On January 21, 2022 draft amendments in New Drugs and Clinical Trials (ND&CT) Rules 2019 called as New Drugs and Clinical Trials (Amendment) Rules, 2022 have been proposed. This includes provisions for deemed approval for various steps involved in the clinical trial for new drugs, including registration of ethics committees, conducting clinical trials and manufacturing new drugs for test or analysis or clinical trials. The following table gives a list of the rules affected along with the subject matter, timeline & introduction of new-concerned Forms. As per the proposed amendment if CLA does not respond within the stipulated time period then the subject matter in the rule concerned shall be deemed to be legally valid & the next steps required shall be undertaken. Several new Forms have been introduced to each subject matter concerned. (11-16)

Table 2. Subsequent amendments in NDCTR 2019

SN	Gazette Notification/Date	Purpose	Explanation
1	Draft GSR 354 (E) dated 5 June 2020 (11)	Compassionate Use of New Drug	CHAPTER XI, Rule 96 Provisions included for compassionate use of any unapproved drug which is undergoing Phase 3 trails either in India or globally by importing or manufacturing it indigenously. This facilitates availability of new drugs which are under phase-II/III studies and provide an acceptable safety profile in clinical trials.
2	Draft GSR 99 (E) dated 5 Feb 2021 Final GSR 605 (E) dated 31 Aug 2021 (12)	For inclusion of provision related to registration of standalone bioanalytical laboratory under NDCTR 2019	Provisions included for registration of stand-alone Bio-analytical laboratories by inserting the word analytical part in the definition as follows - "BA and BE study centre" means a centre created or established to undertake BA study or BE study of a drug for either clinical part or analytical part or for both clinical and analytical part of such study. The existing definition did not covered stand-alone analytical laboratories.
3	Draft GSR 524 (E) dated 2 Aug 2021	Amendment in Eighth Schedule –	Inclusion of word "Designated Registration Authority (DRA)" in place of "Central Licensing Authority (CLA)" (13)

	Final GSR 21 (E) dated 18 Jan 2022	Form CT-03	
4	Draft GSR 767(E) dated 27 Oct 2021 Final GSR 14 (E) dated 13 Jan 2022	To amend Rule 2 to substitute Cell or Stem Cell derived products under NDCTR 2019	The words "stem cell derived products," is proposed to be substituted with "cell or stem cell derived product considering that Cell-based products advanced therapy methods and this should be in line with the growing new drug research and development trends in the industry. (14)
5	Draft GSR 32(E) dated 21 Jan 2022 (15)	Insertion of provision for deemed approvals in various rules under NDCTR 2019	Please refer **Table 3**
6	S.O. 553(E) dated 9 Feb 2022 (16)	Stockpiling of New Drugs under Phase 3 of Clinical Trials	In case a person intends to manufacture and stock a new drug for C-19, which is under clinical trial for marketing authorization for sale or distribution, then such person shall have to obtain permission in Form CT-06 to conduct clinical trial of such drug and on successful completion of the clinical trial and after obtaining permission in Form CT-23 from the Central Licensing Authority under the ND&CT Rules, he shall make an application under Rule 69 or Rule 70A or Rule 75 or Rule 75A of the Drugs Rules, 1945 to the concerned Licensing Authority with the State government. Along with this, the permission should be obtained for conducting clinical trials in Form CT-06 under the ND&CT Rules for grant of license to manufacture and stock the drug for sale or distribution under the provisions of the Drugs and Cosmetics Act, 1940.

Table 3. Provision for deemed approved and various Form numbers with time period

NDCT Rule number	Subject matter	Time Period as per NDCT 2019	Form Number as per deemed approval
Rule 8 , Sub rule 3	Registration to Ethics Committee	Within 45 working days	Form CT-02 A
Rule 22, sub-rule (2)	Grant of permission to conduct clinical trial	Within 90 working days.	Form CT-06 A
Rule 24	Permission to conduct clinical trial of a new drug already approved outside India	Within 90 working days.	Form CT-06 A
Rule 34 , sub rule (2)	Grant of permission to conduct bioavailability or bioequivalence study	Within 90 working days.	Form CT-07 A
Rule 53, in sub-rule(1) and sub-rule (2),	Grant of permission to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study, or for examination, test and analysis.	Within 90 working days.	Form CT 11 A
Rule 60, in sub-rule (1)(ii)	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	Within 90 working days.	Form CT 15A

5. Significance of New Rules

- The first and foremost importance of these rules are that these rules are committed to promote clinical research and innovation in the country. Further, the process is more transparent and approval timelines are faster.
- Well defined, clear, comprehensive, easy to understand and transparent processes have bought clarity in understanding and implementing these rules.
- One of the most important and welcome step bringing more predictability for the approval timelines. Reduced timelines become even more important for drugs for Life threatening diseases, unmet medical need and rare diseases like Cancer.
- Provisions of Accelerated approval, Expedited review and Clinical trial waivers for Life threatening diseases, Unmet medical need and rare disease like Cancer will ensure quicker availability of drugs in the country.
- New compensation clause will bring more ethical practice in the conduct of clinical trials which could be counted as one of the main reason for a steep decline in the number of clinical trials in India. Special preference has been given to safety of trial subjects ensuring that they do not fall victims of the unethical practices followed earlier thus making it simpler and hassle free.
- The unnecessary repetition of trials, wasting huge amount of money and time on things which are

already published or have some data in different countries, thus delaying the availability of new drugs in the country will definitely get reduced with these rules.

- Most importantly, when the whole world is fighting through the difficult times of coronavirus pandemic, these rules are somehow favorable in producing effective and promising medicines in the market to tackle this contagious disease which is the need of the hour.
- Provision of Pre-submission and Post-submissions meetings will Central Licensing Authority is a great step taken in these rules wherein the applicant can get an opportunity before and even after submitting the application to discuss their projects for seeking proper guidance about the requirements and procedures of law for their projects.

6. Conclusion and recommendations

The new rules and the subsequent amendments thereof came up with a variety of neoteric desirable changes that will facilitate clinical research and trials in India. These rules and subsequent amendments have certainly turned out to be very advantageous in terms of faster availability and accessibility of drugs in the country. Further, COVID-19 crisis that is spread across all over the world, with these rules in place will support the Indian pharmaceutical industry to bring a number of medicines which could be promising and effective in treating the patients affected by this deadly virus for which no country in the world has been able to find any cure so far. The clause for local CT waiver, accelerated approval, reduced times for CT application is like a boon for developing new drugs in India. This will ensure faster availability of drugs in the country for life threatening diseases, unmet medical needs and rare disease like Cancer.

Thus, proving it right that NDCT rules and subsequent amendments brought to the rules will be developing the country's reputation across the globe and will harmonize the regulations in line with the International standards. Thus, NDCT rules and subsequent amendments is a significant move and will provide a fillip to the Clinical research and Pharma Industry in India.

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