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Research

Current regulations for clinical trials

M. Parimala*, Unnam Subamoorthy

Department Of Regulatory Affairs, Sree Dattha Institute Of Pharmacy, Nagarjuna Sagar Road Sheriguda, Ibrahimpatnam Rangareddy - 501510.

*Author for Correspondence: M. Parimala
Email: parimalamanusani17@gmail.com

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Abstract

The Clinical Trials Regulation aims to create an environment that is favorable for conducting clinical trials, with the highest standards of patient safety. Clinical trials are investigations in humans intended to discover or verify the effects of one or more investigational medicinal products. Clinical trials are the key tools in new drug evaluation. India has signed the trade related intellectual property rights (TRIPS) agreement as a part of the WTO regulations to gearing up to attract more and more researchers from around the world to conduct clinical trails in India. .For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as per the requirement.

Keywords: Clinical Trials, Regulation, TRIPS, WTO.

INTRODUCTION

Clinical trials are investigations in humans intended to discover or verify the effects of one or more investigational medicinal products. The new Clinical Trials legislation, which was adopted on 16 April 2014 and entered into force on 16 June 2014, has taken the legal form of a Regulation. This will ensure that the rules for conducting clinical trials are identical throughout the EU. This is vital to ensure that Member States, in authorising and supervising the conduct of a clinical trial, base themselves on identical rules. The Clinical Trials Regulation aims to create an environment that is favourable for conducting clinical trials, with the highest standards of patient safety

Aim and objectives

The Clinical Trials Regulation aims to create an environment that is favorable for conducting clinical trials, with the highest standards of patient safety

Objectives

- ✓ Regulations & guidelines
- ✓ Number of Clinical Trial Applications
- ✓ Current initiatives

The main characteristics of the new Regulation are

A streamlined application procedure via a single entry point, the EU portal.
A single set of documents to be prepared and submitted for the application defined in Annex I of the Regulation;
A harmonised procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is jointly assessed by all Member States concerned. Part II is assessed by each Member State concerned separately.
Strictly defined deadlines for the assessment of clinical trial application;
The involvement of the ethics committees in the assessment procedure in accordance with the national law of the Member state concerned but within the overall timelines defined by the Regulation.
Extension of the tacit agreement principle to the whole authorisation process which, without compromising safety, will give sponsors, in particular SMEs and academics, increased legal certainty;
Simplified reporting procedures which will spare sponsors from submitting broadly identical information separately to various bodies and different Member States;
Increased transparency as regards clinical trials and their outcomes;
Union controls in Member states and third countries to ensure that clinical trials rules are being properly supervised and enforced.
Clinical trials conducted outside the EU, but referred to in a clinical trial application within the EU, will have to comply with regulatory requirements that are at least equivalent to those applicable in the EU.

Guidelines

The Commission has and will continue to issue guidance documents in order to ensure a uniform application of the legislation on clinical trials in Europe. The recommendations and guidelines further specifying various aspects of clinical trials, are currently being revised and updated to be in line with the requirements of the Clinical Trials Regulation. The guidelines will be launched for public consultation in sets between Q3 and Q4 of 2016. The aim is to finalise and publish them between the end of 2016 and mid-2017. This section will be updated progressively once the new guidelines are prepared

Transparency

The Clinical Trial Regulation provides more transparency on the clinical trials data. All information in the EU database submitted in the clinical trials application and during the assessment procedure shall be in principle publically accessible unless the confidentiality of the information can be justified on the basis of any of the below listed grounds:
Protection of commercially confidential information;
Protection of personal data;
Protection of confidential communication between the MS in relation to the preparation of the assessment report;
Ensuring effective supervision of the conduct of clinical trial by Member States.
Additionally the Regulation obliges the sponsor to submit to the Database a summary of results and a lay person summary 1 year after the end of the trial in the EU.
A Clinical Summary Report should be submitted to the database 30 days after a Member state grants a Marketing authorisation for the investigational medicinal product, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.

Safety reporting

The Clinical Trial Regulation simplifies the rules on safety reporting:
The protocol may provide that not all adverse events (AE) and serious adverse events are recorded and reported;
For a clinical trial involving more than one investigational medicinal product (IMP) there is the possibility to submit in the Clinical Trial Eudravigilance database a single safety report on all IMPs used in that clinical trial
Suspected unexpected serious adverse reactions (SUSARs) will be reported via the Clinical Trial Eudravigilance database.[1]

Current Regulatory Scenario for Conducting Clinical Trials in India

Current Drug Regulatory Procedures

Currently the clinical trials are regulated by schedule Y of the drug & cosmetics rules, 1945.After the amendment of the D&C act in 2005, the schedule Y was extensively revised to bring the Indian regulations up to par with internationally accepted definitions and procedures. The changes which took place were

• Definitions for Phase I-IV trials, which eliminated the Phase lag
• Clear responsibilities for investigators; and sponsors.
Requirements for notifying changes in protocol
The Central Drugs Standard Control Organization (CDSCO) under Ministry of Health and Family Welfare (MoH and FW) prescribes standards for ensuring safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in India. Apart from these there are other Statutes and ministries that regulate the various aspects of drugs such as; the Poisons Act, 1919; the Pharmacy Act, 1948; the Drug and Magic Remedies (Objectionable Advertisement).

Act, 1954;the Narcotic Drugs and Psychotropic Substances Act, 1985; the Insecticide Act, 1968; The Medicinal and Toilet preparation (Excise duties) Act, 1956 and The Drug (Price Control) Order, 1995 (under the essential commodities Act).Some more laws having a bearing on pharmaceutical manufacture, distribution and sale in India are The Industries (Development and Regulation) Act, 1951,The Trade and Merchandise Marks Act, 1958, The Indian Patent Act, 1970 and the Design Act, 2000 and the Factories Act, 1948

Clinical trials have been defined in Rule 122DAA of the Drugs & Cosmetics Act (D&C Act) in India as "Systemic study of new drugs in human subject(s) to generate data for discovery and/or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetics) and/or adverse effects with the aim of determining safety and/or efficacy of the new drugs.

For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as per the requirement. However for the for new drug substances discovered in countries other than India, Phase I data will be required from the other country and should be submitted along with the application. After submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with Page 3 of 5 other global trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted. Application for permission to start specific phase of clinical trial sponsor is required to submit application (Form 44) for the purpose of conducting clinical trial in India and submit documents as per Schedule Y of the Drugs and Cosmetics Act 1940 and Rules. A clinical trial application utilizes Form 44 as given in table-01, accompanied by documents pertaining to chemical and pharmaceutical information, animal pharmacology, toxicology data and clinical pharmacology data. Other trial-related documents that must be submitted for approval include the Investigator's Brochure, trial protocol, case report form, informed consent form, investigator's undertaking. In addition, the trial's regulatory status of the trial in other countries must be reported. The clinical protocol must be reviewed and approved by an IEC of all participating sites. The requirements in respect of Chemistry and Pharmaceutical information has been elaborated separately for Biologicals while other requirement for conduction of Clinical trial and other requirements remains the same as per Schedule Y of Drugs and Cosmetic Rules 1945.[2]

Clinical Trial Regulations

In most cases, Health Canada is not involved in conducting clinical trial research, but only in the regulation of the sale (distribution) and importation of non-approved drugs for use in human clinical trials. This applies to drugs not marketed in Canada and for approved drugs used outside of the parameters of the Notice of Compliance. As part of that regulatory function, the Therapeutic Products Directorate (TPD) and the Biologics and Genetic Therapies Directorate (BGTD), require that the sponsor (individual, corporate body, institution or organization) undertaking the research, obtain the approval of an appropriate Research Ethics Board before the clinical trial begins, in accordance with the Division 5 of the Food and Drugs Act and Regulations. However, there may be circumstances where Health Canada will be involved in conducting clinical trials. In such situations, an application to Health Canada's Research Ethics Board (REB) for an ethical review of the proposed research by the REB will be required in order to proceed.

Guide to Applicants and NRA reviewers

Requirements for Information on Manufacture of Medicines for Clinical Trials

Applications for clinical trials may be for registered medicines, but for Phase 1, II & III trials, with novel products, many gaps in the knowledge exist regarding the disease process and the recovery from, (or suppression) of infection. Thus trial materials may not be in the form of "products" in their final form, dosage, packaging or even mode of delivery.

Such trials may be considered as "proof of concept", where the new types of product are under evaluation and where the end points are novel and there is little prior knowledge in the field. For example: several of the HIV vaccines, methods of manufacture, delivery, and end points are radically different from other pharmaceuticals or vaccines for which experience and knowledge has accumulated. However, for these "conceptual" materials to be accepted for use in humans, it is important that they adhere as far as possible to the expectations for quality and safety of any medicinal product.

Generally, trials of vaccines are intended to investigate and demonstrate, sequentially, the SAFETY, DOSAGE, IMMUNO-GENICITY and EFFICACY of the product.

It is expected that the medicine used in humans has been:
• Manufactured in a facility under the control, (inspected by) of a competent national regulatory authority and certified as GMP compliant.
• Manufactured under a Quality Assurance program that ensures consistency of product quality.
• Made in suitable facilities with equipment which is qualified, using processes that are validated by staff that are suitably qualified and trained
• Is manufactured to meet defined specifications for raw materials, intermediate and final product
• Shown to meet the specifications using meaningful tests
• Is documented with regard to materials, equipment, methods and tests.
• Shown to be stable for key parameters, in the defined packaging and storage conditions for at least the duration of the trial.
• And that product, manufactured and formulated identically, and meeting the same specifications has been subjected to adequate, comprehensive pre-clinical and toxicological testing The Applicant must satisfy the reviewers that Good Manufacturing Practices are in place, and employed, at all stages of manufacture of the trial vaccine, and must expect that inspectors from the regulatory authority will inspect the sites involved.
It is possible that a current certificate from a suitable competent authority will be acceptable evidence of GMP.

GMP Information for Clinical Trial Evaluation

The following items of information will provide assurance that the quality concerns have been met. The reviewer may request additional information where the applicant has given insufficient or inconsistent information. The detail must relate directly to the medicine to be used in this trial application
1 Names, qualifications & experience of personnel responsible for manufacture, quality assurance,quality control and Final product release
2 Manufacturing site: Addresses and location of each site of manufacture, processing, packaging, storage, test laboratories and Animal facilities used for this product. Some information regarding: layout, finishes, HVAC, product flow, containment, other activities in the same facility and arrangements to prevent contamination of the product. Information on the implementation of documentation: Standard Operating Procedures, Change Control procedures etc.
3 Raw materials:
• Derivation, maintenance and testing of organisms & constructs [Master Seed Characterisation)
• Derivation, maintenance and testing of production substrates cells, tissues or eggs.
• Key raw materials and animal or human derived materials used in the process (prion safety)
• Specifications and tests of materials used during subsequent processing; e.g. inactivation, or
chromatography media and reagents, including materials for regeneration and storage (an indication of the potential toxicity of these materials) - include water quality.
• Specifications of containers and closures.
• Specifications and tests of all materials which are included in the final formulation.
• Where the tests are not pharmacopoeia or similar, then evidence of suitability, consistency and accuracy is required.

4 Manufacturing methods

Explanation in words. If there are deviations from the methods used for product for pre-clinical tests or earlier clinical trial phases, these must be described and explained. Description and/or specifications of equipment used. Flow chart showing steps in the process and sample points with the in-process tests at each step. A description of the in-process tests and limits at each stage. Methods for removal of materials used during preparation, and tests to confirm this. Filling, freeze-drying and packaging methods. Evidence of consistency of manufacture or validation of the processes.

Final product
• Quantities of all constituents in the final product formulation (including limits for residues)
• Specifications for the final product including upper & lower limits of acceptance
• The measure of potency must be defined and justified
• Preservative/s, stabilizer/s and adjuvant/s must be defined and justified.
• Testing methods for demonstrating that the specifications are met. (Reference materials) Where the tests are not pharmacopoeia or similar, then validation information is expected.
• Specifications for the final container and closure. Evidence for suitability .
• Packaging processes, Labelling, transport and storage
• Batch Manufacturing Records for three consecutive recent production lots, made according to the submitted protocol, and including the records for the lot to be used in this trial

Stability
There must be data that demonstrate the stability of the product in the final container and closure, over the proposed time of the trial, and/or a documented program that collects and tests field samples, at all trial sites, to demonstrate that this stability has been achieved during the trial.

Safety
I. Measures to ensure cold-chain maintenance and storage
II. Evidence that the product to be used for the trial is identical in specifications and manufacture to material that has been used in preclinical testing and earlier phases of clinical trials. Where there is uncertainty, this should be described, and the reasons for the changes explained.
III. Measures of waste disposal and disposal of unused product.[3]

Regulations
FDA Regulations Relating to Good Clinical Practice and Clinical Trials
Preambles to GCP Regulations

FDA regulations governing the conduct of clinical trials describe good clinical practices (GCPs) for studies with both human and non-human animal subjects
Electronic Records; Electronic Signatures (21 CFR Part 11)
Regulatory Hearing Before the Food and Drug Administration (21 CFR Part 16)
Protection of Human Subjects (Informed Consent) (21 CFR Part 50)
Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products (21 CFR Parts 50 and 56)
Informed Consent Elements (21 CFR 50.25(c))
Exception From General Requirements for Informed Consent (21 CFR 50.23(e))
Financial Disclosure by Clinical Investigators (21 CFR Part 54)
Institutional Review Boards (21 CFR Part 56)
FDA IRB Registration Rule (21 CFR 56.106)
FDA IRB Registration Rule (21 CFR 56.106) (printable PDF version)
Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR Part 58)
Investigational New Drug Application (21 CFR Part 312)
Foreign Clinical Trials not conducted under an IND (21 CFR 312.120)
Expanded Access to Investigational Drugs for Treatment Use (PDF - 216KB)
Charging for Investigational Drugs (PDF - 204KB)
Form 1571 (Investigational New Drug Application)
Form 1572 (Statement of Investigator)
Applications for FDA Approval to Market a New Drug (21 CFR Part 314)
Bioavailability and Bioequivalence Requirements (21 CFR Part 320)
New Animal Drugs for Investigational Use (21 CFR Part 511)
New Animal Drug Applications (21 CFR Part 514)
Applications for FDA Approval of a Biologic License (21 CFR Part 601)
Investigational Device Exemptions (21 CFR Part 812)
Premarket Approval of Medical Devices (21 CFR Part 814)

Preambles to gcp regulations

Each time Congress enacts a law affecting products regulated by the Food and Drug Administration, the FDA develops rules to implement the law. The FDA takes various steps to develop these rules, including publishing a variety of documents in the Federal Register announcing the FDA's interest in formulating, amending or repealing a rule, and offering the public the opportunity to comment on the agency's proposal. The Federal Register notice explains the legal issues and basis for the proposal, and provides information about how interested persons can submit written data, views, or arguments on the proposal. Any comments that are submitted are addressed in subsequent publications that are part of the agency's decision-making process.

The "preamble" to each of these publications includes all of the printed information immediately preceding the codified regulation. The preamble provides information about the regulation such as why the regulation is being proposed, the FDA's interpretation of the meaning and impact of the proposed regulation, and in those cases where the agency has solicited public comment, the agency's review and commentary on those comments . The preamble can also include an environmental impact assessment, an analysis of the cost impact, comments related to the Paperwork Reduction Act, and the effective date of the implementation or revocation (as the case may be) of the regulation. The documents posted below include the various publications that contributed to the development of final rules related to FDA's regulations on good clinical practice and clinical trials.[4]

A New Regulation for Evolving Needs

Looking to the future, scientific development suggests that future clinical. Trials will target more specific patient populations, such as subgroups identified Through genomic information. In order to include a sufficient number of patients for such clinical trials it may be necessary to involve many, or all, member countries, so any new procedures for the authorization of clinical trials will need to include as many countries as possible under the same rules. Therefore, the European Commission determined to develop a legal Regulation that would repeal the earlier Directive and both simplify the submission of an application dossier for authorization and harmonize the procedures for conducting clinical trials. The goals include:

• Making the European Union more attractive for clinical trial research
• Reversing the decrease in number of investigations of medicines conducted in the EU
• Maintaining high standards of patient safety

Regulation of the European Parliament and of The Council on Clinical Trials on Medicinal Products for Human Use, repealing Directive 2001/20/EC

The new Regulation directly applies to all individuals in the European Union. It was adopted by the European Parliament (02 April 2014) and by the Council of Ministers (14 April 2014) and signed off on 16 April 2014. It was published in the Official Journal on 27 May 2014 and is expected to become effective on 15 June 2016.

First Steps

Two preconditions need to be accomplished by the EMA by January 2016:

• An operational database for clinical trials
• A portal for submissions

Six (6) months after these two components are functional, the Regulation will come into effect.

There will be a transition period of one year, during which trials can be authorized according to the current CT Directive or the new CT Regulation. Trials already authorized in accordance with the current CT Directive will continue to follow the CT Directive until 3 years after the new Regulation comes into effect.

Core Components

The scope of the Regulation is extensive, with several primary components covered in the core text and multiple appendices, including:

• Authorization procedures
• Start of trial, suspension or temporary holds, early termination
• Protection of subjects, informed consent
• Conduct of trials
• Safety reporting
• IMP manufacturing, labeling and import
• Insurance

Country-specific Aspects

Certain aspects are not covered by the Regulation and remain country specific, including:

• Ethics
• Legal representative of the subject not able to provide informed consent
• Substantial rules of liability in the case of damages
• Requirements for investigators and site qualification
• Requirements for country/site specific documents such as originals and copies, notarization, language Additional approvals might still be required for certain items as well, such as:
• R & D in the UK
• CNOM in France
• Radiation approval in Germany when applicable
• Local EC/Authorities
• Data Protection

CONCLUSION

Clinical trials regulated under a legal framework incorporating GCPs

- ✓ CTA required for Phase I, II, III
- ✓ 30 calendar day review period with 2 day turnaround for requests for additional information
- ✓ Ongoing requirements after authorization
- ✓ Clinical trial inspection program

- ✓ ICH guidelines and HC guidance documents
- ✓ Number of CTAs have increased since 2001, but stable since 2004
- ✓ Ongoing HC initiatives impacting on clinical trials

The new EU Regulation on Clinical Trials is expected to be a major Improvement over the previous CT Directive and will:

- ✓ Streamline the approval process for studies conducted across multiple Member States
- ✓ Make one single application sufficient for conducting clinical trials in several Member States
- ✓ Harmonize the regulation of clinical trials throughout the Member States
- ✓ Simplify reporting procedures
- ✓ Increase the transparency of clinical trial results

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