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Research Article

International conference on harmonisation of technical requirements for registration guideline for good clinical practice

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ABSTRACT

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. As positive safety and efficacy data are gathered, the number of patients typically increases. Clinical trials can vary in size, and can involve a single research entity in one country or multiple entities in multiple countries.

Keywords: Clinical trials, Various phases, DGCA.

CLINICAL TRIALS AN OVERVIEW

The first proper clinical trial was conducted by the physician James Lind. The disease scurvy, now known to be caused by a Vitamin C deficiency, would often have terrible effects on the welfare of the crew of long distance voyages. In 1740, the catastrophic result of Anson's circumnavigation attracted much attention in Europe; out of 1900 men, 1400 had died, most of them allegedly from having contracted scurvy. John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an antiscorbutic effect) from the 17th century, but their use did not become widespread [4].

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be

established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any un favorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Independent Ethics Committee (IEC)

An independent body a review board or a committee, institutional, regional, national, or supranational, constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

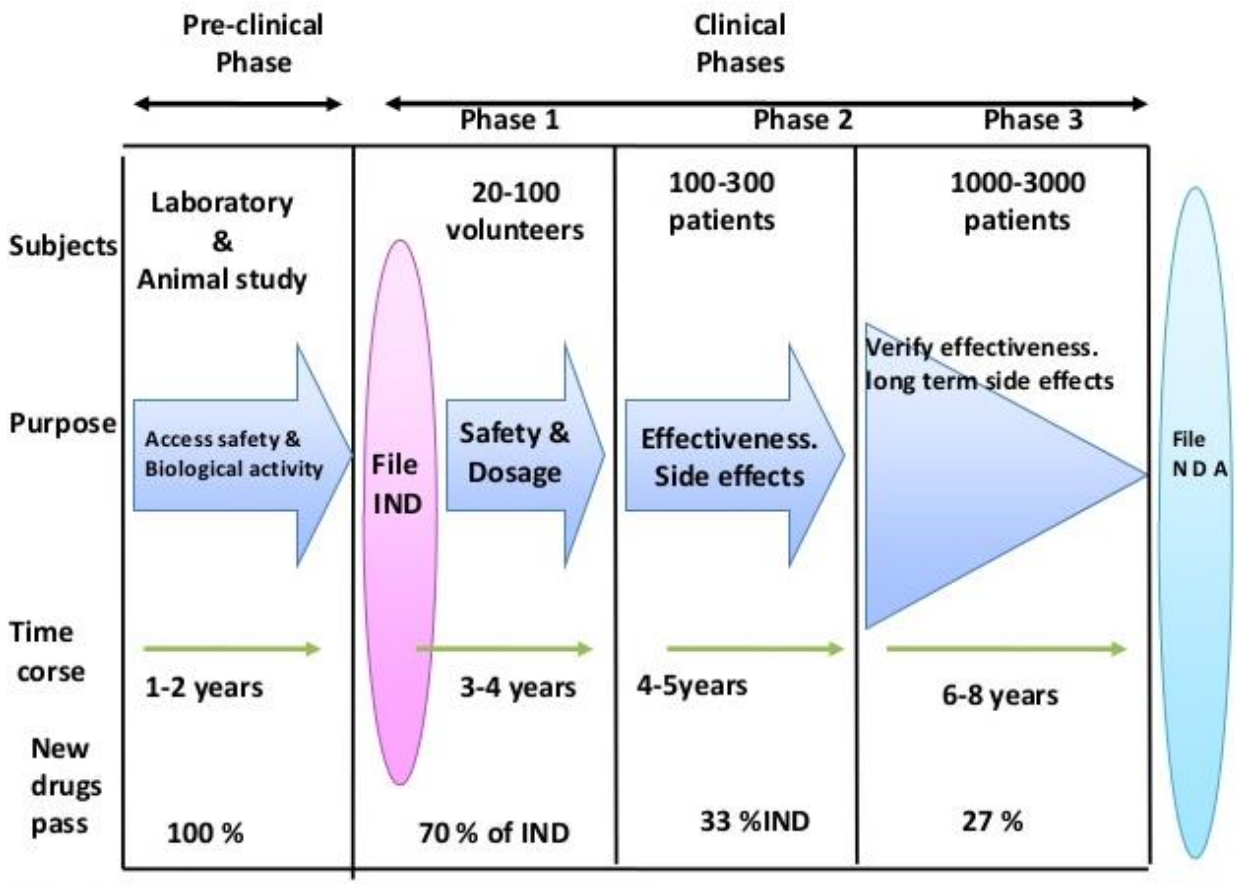

Fig 1: Clinical and pre-clinical phases

PHASES OF CLINICAL TRIALS

Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase I to phase II or from phase II to phase III. Therefore, it may be easier to think of early phase studies and late phase studies. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population. Phase IV are 'post-approval' studies.

A systematic verification of the study, carried out by persons not directly involved, such as:

- Study related activities to determine consistency with the *Protocol*
- Study data to ensure that there are no contradictions on *Source Documents*. The audit should also compare data on the Source Documents with the interim or final report. It should also aim to find out if practices were employed in the development of data that would impair their validity. [9, 10].
- Compliance with the adopted Standard Operating Procedures (*SOPs)*

Blinding / Masking

Case Record Form (CRF)

Clinical Trial (Clinical Study)

Human/Clinical Pharmacology trials (Phase I)

Exploratory trials (Phase II)

In phase II trials a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centers and carried out by clinicians specialized on the concerned therapeutic areas and having

adequate facilities to perform the necessary investigations for efficacy and safety.

Confirmatory trials (Phase III)

Phase IV

Comparator Product

Co-Investigator

Clinical Research Organization (CRO)

An organization to which the sponsor may transfer or delegate some or all of the tasks, duties and / or obligations regarding a Clinical Study. All such contractual transfers of obligations should be defined in writing. A CRO is a scientific body – commercial, academic or other [6].

a. Ethics Committee
b. Final Report
c. Good Clinical Practice (GCP)
d. Impartial Witness
e. Informed Consent
f. Investigator
g. Investigator's Brochure
h. Monitor
i. Multi-Centric Study
j. Principal Investigator
k. Protocol
l. Source Data
m. Sponsor
n. Subject Identification Code
o. Study Management

Steering, supervising, data management and verification, statistical processing and preparation of the study report.

Validation

Regulatory momentum

Timelines

With proper documentation, trial applications can be approved within a relatively short timeline. Making error-free submissions is the key to getting faster approvals from the DCGI [7].

Tab 1: Regulatory Time Lines In India

REGULATORY TIME LINES IN INDIA		
Regulatory body	**Approval**	**Timeline**
DCGI	For conduct of all phases of clinical trials	First response or approval within 45 working days
	For conduct of bioequivalence study for expert	28 working days
IEC/IRB	IEC approval by various study sites	4-6 weeks (in parallel)
DCGI	Test license to import supplies	2 weeks
TOTAL(Parallel processing)	Not applicable	14 weeks
Any files sent to referral bodies/ sent for expert opinion	IND applications for rDNA products, radiopharmaceuticals, stem cells, etc	Additional 12 to 14 weeks

Any inadequacy found in the documents will lead to a query from the DCGI. The applicant's response to the query goes through a long queue and takes time to reach the concerned authority. Any discrepancy could thus delay the process by an additional 45 day

CLINICAL TRIALS IN INDIA: ADVANTAGES AND CHALLENGES[8]

In addition to the efforts mentioned above to align India's regulatory framework and guidelines with international standards, the main advantages of carrying out clinical trials are:

- ✓ Strong availability of study subjects across major therapeutic segments;
- ✓ High level of ICH GCP and US Food and Drug Administration standards compliance (since 2001, the DCGI has implemented conformity to ICH GCP and good laboratory practice guidelines. Generally, most competent authorities, including the US FDA, will find the standards of Indian clinical trials acceptable)
- ✓ High quality of research professionals (India has a strong reputation for graduating students in the medical and scientific fields. The government is involved in curriculum development at major universities and students pursuing these fields of

study are given financial incentives to study in India);

- ✓ A favorable regulatory environment that allows the conduct of global trials, duty-free imports of drugs intended for use in trials, bioequivalence studies for export of data, etc;
- ✓ Cost competitiveness (depending on the number of patients and investigators, and the amount of analytical work completed in India, most sponsors will enjoy a 30-50% cost advantage over a similar trial in Europe or the US6); and
- ✓ Increasing prevalence of diseases.
- ✓ Approval of clinical trial documents from both the IRB/IEC and the DCGI is mandatory to initiate a study. Because India's potential as a major hub for global clinical research has been acknowledged and thus, the regulatory bodies have to elevate themselves to meet international standards, they are facing some challenges. Some of the major issues that have been recognized as areas in need of improvement are discussed below.

Regulatory bodies involved with clinical trials in India

- ✓ The role of regulatory bodies in clinical trials is to ensure quality drug supply and maintaining health and well being of trial participants. In India, the central government's Central Drugs Standard Control Organization under the Ministry of Health and Family Welfare(headed by the Drug Controller General of India) develops standards and regulatory measures for drugs, diagnostics and devices; lays down regulatory measures; and regulates the market authorization of new drugs as per the Drugs and Cosmetics Act . The Department of Chemical and Petrochemicals of Ministry of Chemicals and Fertilisers, through National Pharmaceutical Pricing Authority (NPPA), sets the prices of drugs; maintains data on production, exports and imports; and enforces and monitors the supply of medicines and also gives opinions to parliament on the related issues.[11,12,13.]
- ✓ Other ministries that play an indirect role in regulation include the Ministry of Finance, Ministry of Environment and Forests, Ministry of Science and Technology and the Ministry of Commerce and Industry. Regulation of Patents, drug exports is governed by Department of Industrial Policy and Promotion and Directorate General of Foreign Trade, under the aegis of Ministry of Commerce and Industry and the Ministry of Chemical and Fertilisers respectively. Licensing, quality control and distribution is maintained by the CDSCO, Ministry of Health and Family Welfare, Department of Biotechnology, Ministry of Science and Technology (DST) and Department of Environment. Drug Controller General of India (DCGI) handles the approval of licenses of specified categories of drugs such as I. V. Fluids, vaccines, sera, blood and blood products.
- ✓ The CDSCO office regulates the clinical trials via its central office at New Delhi and four zonal offices situated at Mumbai, Chennai, Kolkata and Ghaziabad. These zonal offices work in close collaboration with the state offices to bring about uniform enforcement of the regulations imposed by the central government.

- Lengthy approval timelines
- Inspections by health authorities
- Manpower crunch and application backlog
- Lack of communication:
- PREREQUISITES FOR THE STUDY:
- Investigational Pharmaceutical Product:
- Pre-clinical supporting data

Protocol

A well designed study relies predominantly on a thoroughly considered, well-structuredand complete protocol.

1. Relevant components of Protocol
2. General information

a. Protocol title, protocol identifying number and date. All amendments should bear amendment number and date(s)

b. Name, address & contact numbers of the sponsor and the monitor / CRO

c. Name and title of the persons authorized to sign the protocol and the protocol amendments for the sponsor

d. Name, title, address and contact numbers of the sponsor's medical expert for the study

e. Name(s), title(s), address (es) and contact numbers of the investigator(s) who is / are responsible for conducting the study, along with their consent letter(s)

f. Name(s), address (es) and contact numbers of the institution(s) clinical laboratories and / or

other medical and technical departments along with the particulars of the head(s) of the institution(s) and the relevant department(s)

Objectives and Justification

a. Aims and objectives of the study, indicating the Phase to which the study corresponds
b. Name and description of the investigational product(s)
c. A summary of findings from non-clinical studies that potentially have clinical significance and from clinical studies that is relevant to the study
d. Summary of the known and potential risks and benefits, if any, to human subjects
e. Description of and justification for the route of administration, dosage regimen and treatment periods for the pharmaceutical product being studied and the product being used as control. Dose-response relationships should be considered and stated.
f. A statement that the study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements
g. Description of the inclusion & exclusion criteria of the study population
h. References to the literature and data that are relevant to the study and that provide background for the study**.**

Ethical Considerations

a. General ethical considerations related to the study
b. Description of how patients / healthy volunteers will be informed and how their consent will be obtained
c. Possible reasons for not seeking informed consent

Study design

The scientific integrity of the study and the credibility of the data from the study depend substantially on the study design.

Description of the study design should include

a. Specific statement of primary and secondary end points, if any, to be measured during the study
b. Description of the type of the study (randomized, comparative, blinded, open, placebo controlled), study design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), randomization (method and procedure) and placebo controlled. [14, 15]
c. A schematic diagram of the study design, procedures and stages
d. Medications/treatments permitted (including rescue medications) and not permitted before and / or during the study
e. A description of the study treatments, dosage regimen, route of administration and the dosage form of the investigational product and the control proposed during the study
f. A description of the manner of packaging and labeling of the investigational product
g. Duration of the subject participation and a description of the sequence of all study periods including follow-up, if any
h. Proposed date of initiation of the study
i. Justification of the time-schedules e.g. in the light of how far the safety of the active ingredients, medicinal products has been tested, the time course of the disease in question
j. Discontinuation criteria for study subjects and instructions on terminating or suspending the whole study or a part of the study
k. Accountability procedures for the investigational products including the comparator product
l. Maintenance of study treatment randomization codes and procedures for breaking codes
m. Documentation of any decoding that may occur during the study
n. Procedures for monitoring subjects' compliance

Inclusion, Exclusion and Withdrawal of Subjects

a. Subject inclusion criteria: specifications of the subjects (patients / healthy volunteers) including age, gender, ethnic groups, prognostic factors, diagnostic admission criteria etc. should be clearly mentioned where relevant.
b. Subject exclusion criteria, including an exhaustive statement on criteria for pre-admission exclusions
c. Subject withdrawal criteria (i.e. terminating investigational product treatment / study treatment) and procedures specifying when and how to withdraw subjects from the treatment, type and timing of the data to be collected from withdrawn subjects, whether and how subjects

are to be replaced and the follow-up on the withdrawn subjects. [16, 17]

d. Statistical justification for the number of Subjects to be included in the Study

Handling of the Product(s)

a. Measures to be implemented to ensure the safe handling and storage of the pharmaceutical products.
b. System to be followed for labeling of the product(s) (code numbering etc.)
c. The label should necessarily contain the following information: the words - "For Clinical Studies only", the name or a code number of the study, name and contact numbers of the investigator, name of the institution, subject's identification code.

Assessment of Efficacy

a. Specifications of the effect parameters to be used
b. Description of how effects are measured and recorded
c. Time and periodicity of effect recording
d. Description of special analyses and / tests to be carried out (pharmacokinetic, clinical, laboratory, radiological etc.)

Assessment of Safety

a. Specifications of safety parameters
b. Methods and periodicity for assessing and recording safety parameters
c. Procedures for eliciting reports of and for recording and reporting adverse drug reactions and / or adverse events and inter-current illnesses
d. Type and duration of the follow-up of the subjects after adverse events
e. Information on establishment of the study-code, where it will be kept and when, how and by whom it can be broken in the event of an emergency

Statistics

a. Description of the statistical methods to be employed, including timing of any planned interim analysis
b. Number of study subjects needed to achieve the study objective, and statistical considerations on which the proposed number of subjects is based
c. Detailed break-up of the number of subjects planned to be enrolled at each study site (in case of multi-center studies)
d. The level of statistical significance to be used
e. Procedures for managing missing data, unused data and unauthentic data
f. Procedures for reporting any deviations from the original statistical plan (any deviations from the original statistical plan should be stated and justified in protocol and / in the final report, as appropriate)
g. Selection of the subjects to be included in the final analyses (e.g. all randomized subjects / all dosed subjects / all eligible subjects / evaluable subjects. [17,18,19]

Data handling and management

A statement should be clearly made in the protocol that "The investigator(s) / institution(s) will permit study related monitoring, audits, ethics committee review and regulatory inspection(s) providing direct access to source data / documents".

a. A copy of the CRF should be included in the protocol. Besides, the following details should be given:
b. Procedures for handling and processing records of effects and adverse events to the product(s) under study
a. Procedures for the keeping of patient lists and patient records for each individual taking part in the study. Records should facilitate easy identification of the individual subjects.

Quality control and quality assurance

a. A meticulous and specified plan for the various steps and procedures for the purpose of controlling and monitoring the study most effectively
b. Specifications and instructions for anticipated deviations from the protocol
c. Allocation of duties and responsibilities with-in the research team and their co-ordination
d. Instructions to staff including study description (the way the study is to be conducted and the procedures for drug usage and administration)
e. Addresses and contact numbers etc. enabling any staff member to contact the research team at any hour

f. Considerations of confidentiality problems, if any arise
g. Quality control of methods and evaluation procedures

Finance and insurance

a. All financial aspects of conducting and reporting a study may be arranged and a budget made out.
b. Information should be available about the sources of economic support (e.g. foundations, private or public funds, sponsor / manufacturer). Likewise it should be stated how the expenditures should be distributed e.g. payment to subjects, refunding expenses of the subjects, payments for special tests, technical assistance, purchase of apparatus, possible fee to or reimbursement of the members of the research team, payment of the investigator / institution etc.)
c. The financial arrangement between the sponsor, the individual researcher(s) / manufacturer involved, institution and the investigator(s) in case such information is not stated explicitly
d. Study Subjects should be satisfactorily insured against any injury caused by the study
e. The liability of the involved parties (investigator, sponsor / manufacturer, institution(s) etc.) must be clearly agreed and stated before the start of the study

Publication policy

A publication policy, if not addressed in a separate agreement, should be described in the protocol.

Evaluation

a. A specified account for how the response is to be evaluated
b. Methods of computation and calculation of effects
c. Description of how to deal with and report subjects withdrawn from / dropped out of the study

Supplementaries and appendices

The following documents should be appended with the protocol:

a. Information to the Study Subjects and the mode of providing it
b. Instructions to staff
c. Descriptions of special procedures

ETHICAL & SAFETY CONSIDERATIONS [8]

Ethical Principles

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current revision of Declaration of Helsinki (see Appendix 1) and should respect three basic principles, namely justice, respect for persons, beneficence (to maximize benefits and to minimize harms and wrongs) and non maleficence (to do no harm) as defined by "Ethical Guidelines for Biomedical Research on Human Subjects" issued by the Indian Council of Medical Research and any other laws and regulations of the country, which ensure a greater protection for subjects. [20]

The following principles are to be followed:

a. Principles of essentiality
b. Principles of voluntariness
c. Principles of non-exploitation
d. Principles of privacy and confidentiality
e. Principles of precaution and risk minimization
f. Principles of professional competence
g. Principles of accountability and transparency
h. Principles of the maximization of the public interest and of distributive justice
i. Principles of institutional arrangements
j. Principles of public domain
k. Principles of totality of responsibility
l. Principles of compliance

Ethics Committee

Basic Responsibilities

Composition

Terms of Reference

Review Procedures

The Ethics Committee should review every research proposal on human subjects. It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the subjects with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues.

The ethical review should be done through formal meetings and should not resort to decisions through circulation of proposals.

- Submission of Application:
- Decision Making Process
- Interim Review
- Record Keeping
- Special Considerations
- Informed Consent Process
- Informed Consent of Subject
- Essential information for prospective research on subjects
- Compensation for Participation
- Selection of Special Groups as Research Subject
- Pregnant or nursing women
- Children
- Vulnerable groups
- Compensation for Accidental Injury
- Obligation of the sponsor to pay
- Approval of New Drug in India

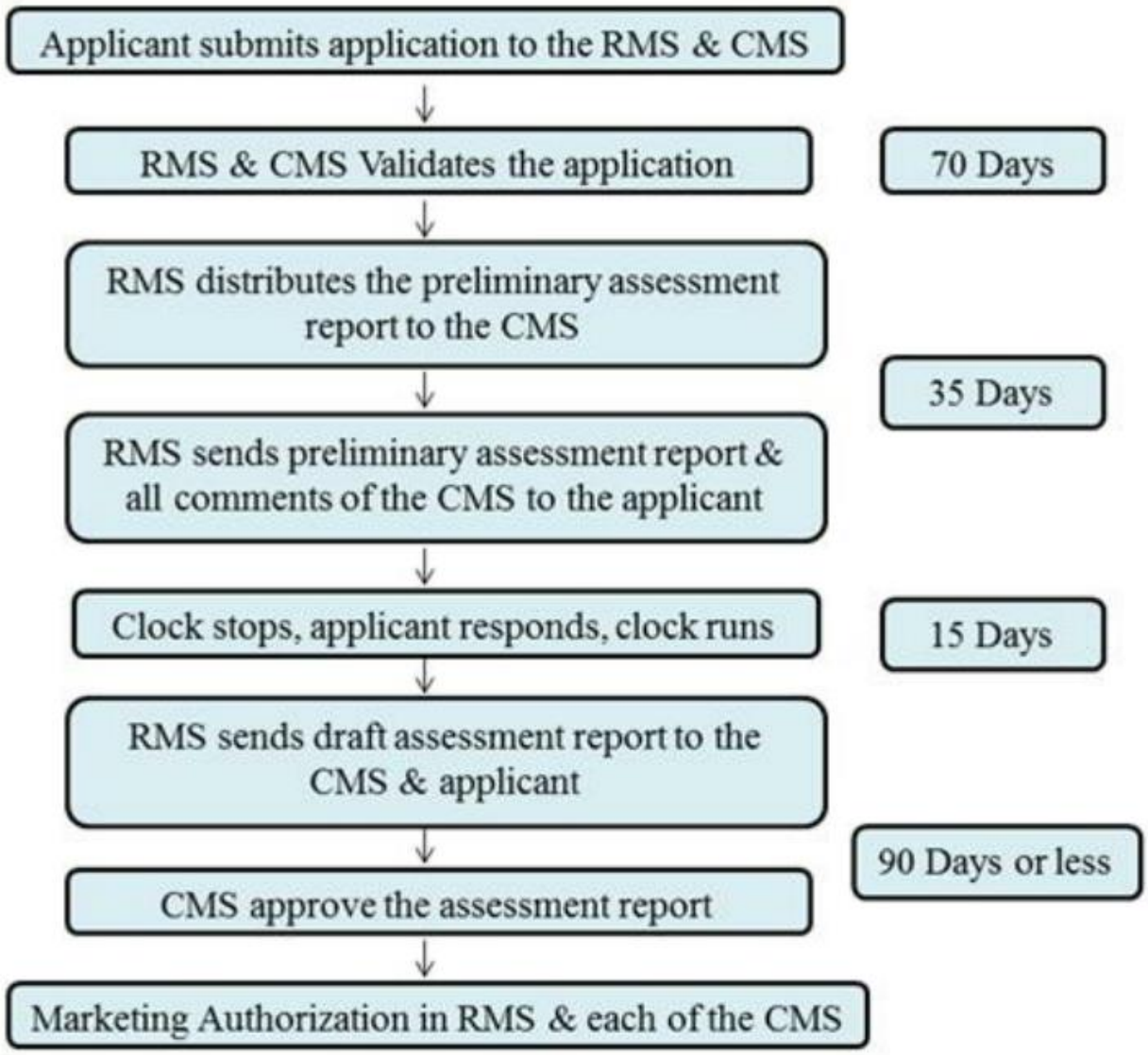

Fig 2: Flow chart of Decentralized Procedure

Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required. Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances

which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials. Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that the licensing authority may require pharmacokinetic studies (Bioequivalence studies) first to show that the data generated in Indian population is equal to data generated abroad and then require him to proceed with Phase III trials. In summary, the exact requirements of Clinical trials may change from case to case and depend on the extent to which licensing authority is satisfied about its safety and efficacy. The process of approval of new drug in India is a very complicated process, which should meet necessary requirements along with NDA to FDA. The need of the present work is to study and document the requirements for the process of approval of new drug in India with emphasis on clinical trials as per Drugs Control department, Government of India.

COMPARATIVE STUDIES IN DRUG REGULATION AMONG INDIA, US AND EUROPE

Tab 2: Principal difference between India, US and Europe

Principal differences between US, EU, & India

Requirements	US	EU	INDIA
Agency	One Agency USFDA	Multiple Agencies EMEA CHMP National Health Agencies	One Agency DCGI
Registration Process	One Registration Process	Multiple Registration Process 1. Centralized (E.U - Community) 2. Decentralized (At least 2 member states) 3. Mutual Recognition (At least 2 member states) 4. National (1 member state)	One Registration Process
Application	ANDA / NDA	MAA	MAA
Debarment classification	Required	Not Required	Not Required
Number of copies	3	1	1
Approval Timeline	~18 Months	~12 Months	12 - 18 Months
Fees	Under $2 million-NDA Application $51,520 – ANDA Application	National fee (including hybrid applications): £103,059 Decentralised procedure where UK is CMS: £99,507	50,000 INR

Administrative Requirements between India, US and Europe

The administrative requirements between India, US and Europe are mentioned below

REQUIREMENTS	USA	EU	INDIA
ADMINISTRATIVE			
Application	ANDA	MAA	MAA
Debarment Certification	Required	NA	NA
No. of copies	3	1	1
Approval time line	18 Month	12 Month	12 Month
Fees	No Fees	10-20 Lakh	50,000
Presentation	eCTD & Paper	eCTD	Paper
FINISHED PRODUCT CONTROL			
Justification	ICHQ6A	ICHQ6A	ICHQ6A

Fig 5: Administrative Requirements between India, US and Europe

REQUIREMENT	USA	EU	INDIA
Assay	90-100%	95-105%	90-110%
Disintegration	Not required	Required	Required
Color Identification	Not required	Required	Required
Water content	Required	Not Required	Required
MANUFACTURING & CONTROL			
No. of batches	01	03	1
Packaging	A min of 1,00,000 Units	Not Required	-
Process validation	Not required at the time of submission	Required	Required
Batch size	Min of 1,00,000 Units	Min of 1,00,000 Units	Not Specified

Fig 6: Finished Product Control Requirements and Manufacturing & Control Requirements

Requirement	USA	EU	India
STABILITY			
No. of batches	01	02	01
Condition	25/60: 40/75	25/60: 40/75	30/35; 30/70
Date & Time of submission	3 Month Accelerate & 3 Month Long term	6 Month Accelerate & 6 Month Long term	6 Month accelerated & 3 Month Long term
Container orientation	Inverted & Upright	Do not address	Do not address
Clause	21CFR Part 210 & 211	Volume4, EU guidelines for medicinal product	ICHQ1F
QP Certification	Not Required	Required	Required

Fig 7: Stability requirements

REQUIREMENT	USA	EU	INDIA
BIOEQUIVALENCE			
CRO	Audited by FDA	Audited by MHRA	CDSCO
Reserve sample	5 Times the sample required for analysis	No such requirement	-
Fasted/Fed	Must be as per OGD recommendation	NO such requirement	As CDSCO recommendation
Retention of samples	5 Year from the date of filing the application	No such requirement but usually followed	3 years from date of filing the application

Fig 8: Bioequivalence Requirements

CONCLUSION

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

The overall aim of this Publications is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

REFERENCES

[1]. Tribulations Second Edition, M edited by Allen Cato, Lynda Sutton, Cato Research Ltd. Durham, North Carolina, Allen Cato III, Cato Research Ltd. San Diego, California 2002 Marcel Dekker, Inc. Marcel Dekker, Inc. New York • Basel
[2]. Clinical Research in Pharmaceutical Development, edited by Barry Bleidt and Michael Montagne c 2002 Marcel Dekker, Inc. Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016
[3]. Drug Products for Clinical Trials: An International Guide to Formulation, Production, Quality Control, edited by Donald C. Monk house and Christopher T. Rhodes Marcel Dekker, Inc. New York.
[4]. RNCOS, Booming Clinical Trials Market in India, September 2009, www.rncos.com/Report/IM564.htm
[5]. CDSCO, Good Clinical Practices for Clinical Research in India, Schedule Y (Amended Version – 2005),
[6]. http://cdsco.nic.in/html/GCP1.html
[7]. 3. ICMR, Ethical Guidelines for Biomedical Research on Human Participants, 2006,
[8]. www.icmr.nic.in/ethical_guidelines.pdf
[9]. CDSCO, Guidance for Industry, Document No CT/71108, Version 1.1,
[10]. http://cdsco.nic.in/CDSCO-GuidanceForIndustry.pdf
[11]. Suvarna et al. World Journal of Pharmacy and Pharmaceutical Sciences 4(7), 2015.
[12]. Marie Miossec and Pierre Miossec New Regulatory Rules for Clinical Trials in the United States and the European Union Arthritis & Rheumatism 54(12), 2006, 3735–3740
[13]. Prajapati Vishal, Goswami Rahulgiri, Makvana Pratik, Badjatya Jitendra Kumar A Review On Drug Approval Process For Us, Europe And India International Journal of Drug Regulatory Affairs;, 2(1), 2014, 1- 11.