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Editorial

Drug Discovery to Drug Approval through Clinical Trials: A Review

Anjan Kumar Mahapatra, Ghanshyam Panigrahi
P.G. Department of Pharmaceutics and P.G. Department of Pharmacology,
Royal College of Pharmacy and Health Sciences, Berhampur-760002, Odisha, India.

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ABSTRACT

The practice of the drug discovery process has been revolutionized with the advancement of newer techniques. Target based drug design is more advantageous, time saving and effective. With the use of combinatorial chemistry and high throughput screening (HTS) techniques, a large number of compounds are synthesized and screened. Quantitative structure activity relationships (QSAR) constitute immense importance in discovering new drug candidate called analogues showing affinity with the target. Preclinical studies in animal determine safety and effectiveness of the drug under controlled environment. Clinical trials, often called "the gold standard" are the most perfect tool for evaluation of the applicability of the clinical research. Clinical trials can be performed, after an application is submitted to competent authority of the concerned country. The competent authority reviews an application submitted to get approval for marketing the drug and approves if satisfied with the quality, safety and efficacy aspects. Though certain aspects of drug approval process are similar among different countries, some differences do occur. To overcome the difficulties due to these differences in various countries, the practice of common technical document (CTD) has been introduced by the international conference on harmonization (ICH). This review shall give an updated insight of the title; Drug discovery to drug approval through clinical trials.

*Corresponding author:
Dr. Anjan Kumar Mahapatra,
P.G. Department of Pharmaceutics, Royal College of Pharmacy and Health Sciences,
Berhampur-760002, Odisha, India. **E-mail**: anjanmahapatra@gmail.com

Background

For thousands of years most drugs were crude natural products of unknown composition and limited efficacy. Although human civilization has been experimenting and consuming drugs for many centuries, it is only in the past 10 decades that the foundation was laid for the systematic research and development of drugs. The process of drug discovery and development can be broadly categorized into two subclasses: drug discovery and drug development. The drug discovery process can be described as the identification and validation of a disease target and search or synthesize of a chemical or biological compounds to interact with that target. This interaction can be to block, promote or otherwise modify the activity of the target [1]. The drug discovery processes involve finding leading drug candidates for further development. Drug development involves satisfying all requirements that have to be met before a new compound can be deemed ready for testing in human subjects for the first time. Drug testing is achieved by preclinical and clinical trials.

Modern drug discovery and development

The process from discovering a new drug to registering it for marketing and commercialization is a challenging, time consuming and expensive. The process of drug discovery takes about 15 years to complete, and the interesting feature is that it is complete only for few drug candidates as large number of parameters has to follow in order to pass from each and every step. Currently, the research and development cost of each molecular entity is approximately US $1.8 billion [2]. Success rate in getting from an initial compound to an approved and commercially available product is very low. Typically, tens of thousands of compounds are screened and tested, and only a handful makes it onto the market as drug products.

Key stages of modern drug discovery and development:

Drug discovery and development stages involve the following steps:

Drug discovery

1. *Selection of program*
2. *Target identification*
3. *Target validation*
4. *Assay development*
5. *Hit to lead selection*
6. *Lead optimization*
7. *Identification of a drug candidate*

Drug Development

1. *Preclinical study*
2. *Clinical trials*
3. *Release of the drug*
4. *Follow-up monitoring*

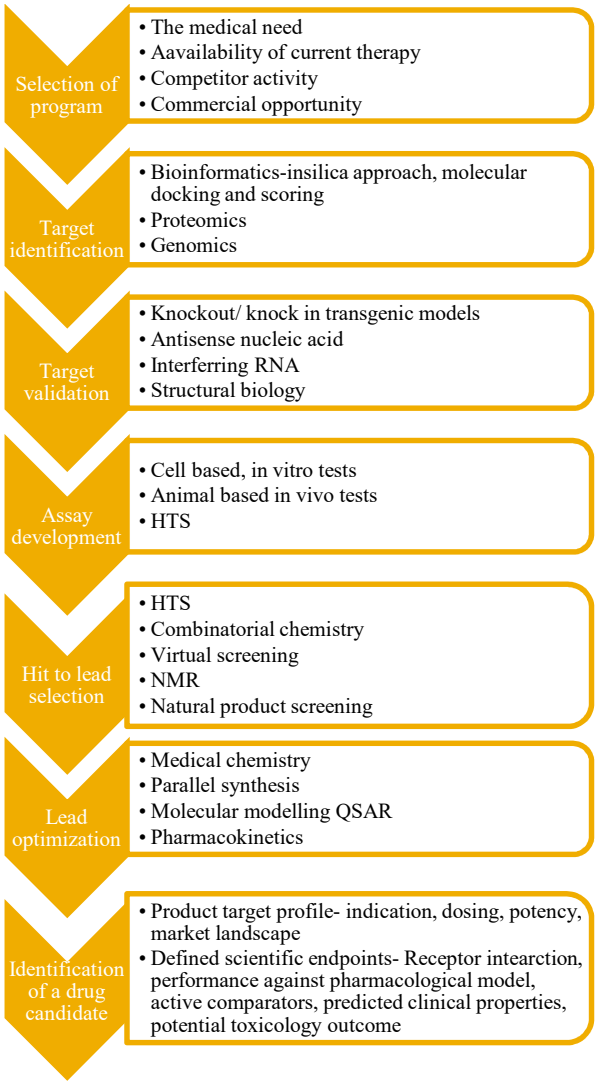


Figure 1: Key stages of drug discovery

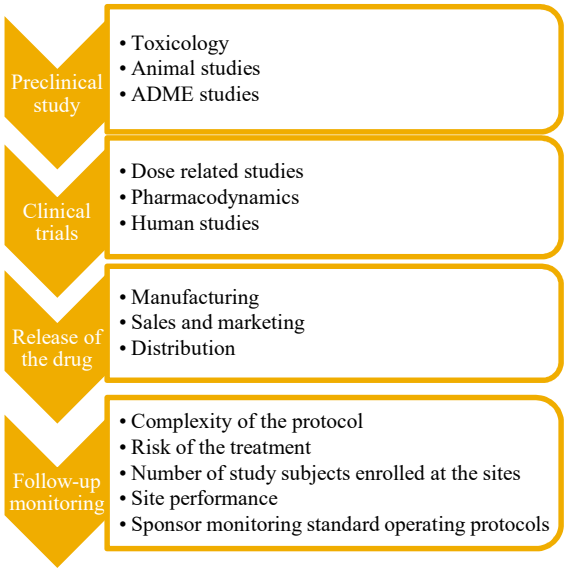


Figure 2: Key stages of drug development

Selection of program

Before experimental work starts a clear strategy is needed for choosing a disease to work on and selection of a disease target. In the early days there were many therapeutic opportunities but no acceptable therapies; which are available now for many conditions. Therefore, the new agents shall clinically effective with statistically significant advantages over existing therapy. In proposing a new research project; one should consider:

i. The medical need (life threatening or self-limiting condition).
ii. Availability of current therapy (The level of satisfaction is high or low).
iii. Competitor activity (whether the new drug: show increased selectivity for a particular biological mechanism or permit a novel approach to the management of the disease).
iv. Commercial opportunity (potential market and duration of the proposed therapy).

Target identification

Targets are the specific components naturally existing cellular or molecular structure involved in the pathology which is responsible for disease; they may be receptors, enzymes, nucleic acids, hormones, ion channels etc. Target selection by the investigator depends on the disease on which he focused. Many new scientific approaches are now used to

determine targets (most targets are receptors or enzymes) and obtain the lead compounds; including the use of genomic technology, synthetic chemistry, recombinant DNA (rDNA) technology, laboratory automation and bioinformatics. For identification of target, In Silico drug design approach is widely used, which involves use of computer for the identification of the drug target molecule by employing bioinformatics tools [3]. Molecular docking and scoring techniques are also widely used; it involves computationally placing a virtual molecular structure into a binding site of a biological macromolecule. Various software's have been developed- Autodock, Zdock, Dock and Docking server.

Target validation

It involves demonstrating relevance and confirmation of the target protein in a disease process. Target validation requires a demonstration that a molecular target is critically involved in a disease process and that modulation of the target is likely to have a therapeutic effect. In this regard transgenic models are used; one with the target (knock in/ gain of function) and another without the target (knock out/loss of function) with these models' validation of target is performed. Knock in is used to develop diseased model and sometime knock in models are fatal and lead to death. Various neurodegenerative, disease models have been generated by introducing mutant genes that cause autosomal-dominant forms of the disease in humans [4]. After identifying the mechanism of the diseases, it leads to the formulation of the drug compound which shows interaction with the target.

Assay development

The new chemical entity or molecule is obtained by organic synthesis or molecular modification or isolation from plants. The testing of a (series of) molecule(s) against a known biological target that correlates with a cellular or pharmacological activity is known as screening e.g., enzyme inhibition or receptor binding. This is now made possible or easier in modern research because: macromolecular targets (enzymes / receptors) can be identified; targets are now available in large quantities using molecular biology and automated (HTS) technologies. Genomics, robotics, miniaturization and information technology have accelerated the discovery of novel drug candidates.

Hit to lead selection

Early drug discovery involves several phases from target identification to preclinical development. The identification of small molecule modulators of protein function and the process of transforming these into high-content lead series are key activities in modern drug discovery [5]. Most commonly hit compounds are derived

by High-Throughput Screening (HTS). HTS a high-tech approach for drug discovery in current trend to show how selective the compounds are for the chosen target, and it is more and more gaining popularity among industrial researchers [6]. It is a robust assay that leads to rapid identification of true hits. Typical HTS programs have potentials to screening up to 10000 compounds per day, while some laboratories with Ultra High-Throughput Screening (UTHS) can perform 100,000 assays per day [7]. In addition, once a library of compounds has been established, the same library can be run through many different assays. In practice, because HTS places a premium on rapid assays, false positive and false negative are not uncommon; besides when a true hit is found it is most likely be refined to increase its binding affinity or to change its pharmacological properties (specificity, solubility, stability, kinetic, etc.). This process is called hit-to-lead development.

Lead optimization

It follows the lead finding process. The aim of lead optimization to synthesize lead compounds, new analogs with improved potency, reduce off-target activities, as well as to optimize this with respect to other properties such as selectivity, metabolic stability etc. This optimization is accomplished through chemical modification of the hit structure, with modifications chosen by employing structure activity relationship (SAR) as well as structure-based design if structural information about the target is available [8].

Identification of a drug candidate

The optimized lead compounds are identified as new drug candidates. The quality of a new drug candidate is measured by their success in preclinical and clinical development and finally emerged as active pharmaceutical ingredients (APIs) [8].

DRUG DEVELOPMENT

Once a new chemical identity is discovered it has to be subjected to the development process. Chemical synthetic ability is mostly carried out in the research and development divisions of the pharmaceutical companies. The study of the promising compound can be divided into two stages i.e., preclinical Pharmacology (animal studies) and clinical Pharmacology (human studies).

Preclinical Studies [9]

Pre-clinical studies involve *in vitro* and *in vivo* experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug (IND).

Ethical Requirements for Preclinical Studies

CPCSEA guideline:

Research and experimentation on animals are carried out by short term and long term basis, which are covered by provisions of the prevention of cruelty to animals' act, 1960 (amended in 1982) and rules of breeding of and experiments on animals (Control and Supervision) 1998 (amended in 2001 and 2006) framed under the PCA 1960, Government has constituted a committee for the purpose of control and supervision of Section 15 of PCA Act 1960. The animal house facility should be registered with Committee for purpose of Control and Supervision of Experiments on Animals (CPCSEA). Institutional Animal Ethics Committee (IAEC) and Institutional Biosafety Committee (IBSC) are the local body, approved by CPCSEA.

IAEC has been empowered to permit experiments on small animals through an amendment in rules for breeding and experiments on animals (control & supervision) in year 2006. The IAEC will ensure implementations of all the requirements for a particular project including type of animals, number of animals, handling of animals and adequate skill to perform the experiments and their disposal after use.

The Institutional Biosafety Committee is engaged in hazardous chemical use, genetic engineering research and production activities. This committee shall also examine the proposal on animal experiments involving hazardous agents in addition to its existing functions. IBSC whose members are knowledgeable about hazardous agents, are in place in most of the higher level education, research institutes and in many pharmaceutical industries for safety issues. Institutional Biosafety Committee (IBSC) is to be constituted in all centers engaged in genetic engineering research and production activities.

OECD and ICH guideline:

The Organization for Economic Cooperation and Development (OECD) is an intergovernmental organization in which representative of 29 industrialized countries in North America, Europe and the Pacific, as well as the European Commission, meets to coordinate and harmonize policies, discuss issues of mutual concern, and work together to respond to international problems. The International Conference on Harmonization (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The objective of such harmonization is a more economical use of human, animal and material resources, and

the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

Clinical Studies

A clinical trial is a research study that tests a new medical treatment or a new way of using an existing treatment to see if it will be a better way to prevent and screen for diagnose or treat a disease [10]. The evolution of the modern clinical trial dates back to the eighteenth century [11, 12]. A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention. We define a clinical trial as a prospective study comparing the effect and value of intervention(s) against a control in human beings. It is only in the past several decades that the clinical trial has emerged as the preferred method in the evaluation of medical interventions [13-22].

Types of clinical trials [23]**:**

1. Treatment trials- Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
2. Prevention trials- Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.
3. Diagnostic trials- Conducted to find better tests or procedures for diagnosing a particular disease or condition.
4. Screening trials- Test the best way to detect certain diseases or health conditions.
5. Quality of Life - Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

Phases of clinical trials [24-30]

Clinical trials involving new drugs are commonly classified into four phases. Each phase of the drug approval process is treated as a separate trial. 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[24]. Now Phase 0 or micro dosing studies are performed to know the action of drug candidate in human being at early.

Phase 0

Phase 0 is a recent designation for exploratory, first in- human trials conducted in accordance with the United States Food and Drug Administration's (USFDA) 2006 Guidance on Exploratory IND Studies [31]. Phase 0 trials are also known as human micro dosing studies and are designed to speed up the development

of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies. Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics and pharmacodynamics.

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/ no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data. Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement.

Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small group of healthy volunteers (20-80) will be selected. This phase includes trials designed to assess the safety (Pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an in-patient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials.

There are different kinds of Phase I trials:

SAD: Single ascending dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have

reached the Maximum tolerated dose (MTD).

MAD: Multiple ascending dose studies are conducted to better understand the pharmacokinetics and pharmacodynamics of multiple doses of the drug. In these studies, a group of patients receives multiple low doses of the drug, whilst samples (blood and other fluids) are collected at various time points and analyzed to understand how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level.

Food effect: A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug on different occasions; one while fasted, and one after being fed.

Phase II

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (100-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements (how much drug should be given). Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity. Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized clinical trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

Phase III

Phase III studies are randomized controlled multicenter trials on large patient groups (800-3000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the

appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as "Phase IIIB studies."

While not required in all cases, it is typically expected that there be at least two successful Phase III trials demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (USA), TGA (Australia), EMEA (European Union), or CDSCO/ICMR (India). Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market [32].

Phase IV

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to

certain uses: recent examples involve cerivastatin (Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).

Monitoring clinical trials:

The purposes of trial monitoring are to verify that:

i. The rights and wellbeing of human subjects are protected.
ii. The reported trial data are protected.
iii. The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with good clinical practice (GCP), and with the applicable regulatory requirement(s).

Compliance with protocol

The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority (ies) and which were given approval/ favorable opinion by the IRB/IEC. The investigator/ institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement [36].

The investigator should not implement in deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval / favorable opinion from the IRB / IES of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subject, or when the change(s) involves only logistical or administrative aspect of the trial (e.g., change in monitor (s), change of telephone no.(s).

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/ favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate, the proposed protocol amendment(s) should be submitted.

i. To the IRB/IEC for review and approval/favorable opinion.
ii. To the sponsor for agreement.
iii. To the regulatory authority (IES).

Application forms that are needed to be submitted to FDA (Investigational new drug (IND) / Clinical trial exception (CTX) / Clinical trial authorization (CTA) application)

INDs (in the U.S.), CTXs (in the U.K.) and CTAs (in Australia) are examples of requests submitted to appropriate regulatory authorities for permission to conduct investigational research. This research can include testing of a new dosage form or new use of a drug already approved to be marketed.

In addition to obtaining permission from appropriate regulatory authorities, an Institutional or Independent Review Board (IRB) or Ethical Advisory Board must approve the protocol for testing as well as the informed consent documents that volunteers sign prior to participating in a clinical study. An IRB is an independent committee of physicians, community advocates and others that ensures a clinical trial is ethical and the rights of study participants are protected [37].

Types of IND [37]:

i. ***An Investigator IND****:* It is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

ii. ***Emergency Use IND****:* This allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND.

iii. ***Treatment IND****:* It is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

The two IND categories are *commercial and research (non-commercial)* types. The IND application must contain information in three broad areas: (1) Animal Pharmacology and Toxicology Studies, (2) Manufacturing Information and (3) Clinical Protocols and Investigator Information. Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

IND content and format:

The requirements for the content and format of IND application are given in the 21 Code of Federal Regulations (CFR), Section 312. A sponsor (commercial organization) or an investigator who intends to conduct a clinical investigation should submit an "Investigational New Drug Application" in the following order:

- Form FDA 1571
- Table of contents
- Introductory statement and investigational plan
- Investigator's brochure
- Protocols
- Chemistry, manufacturing and control (CMC) information

- Pharmacology and toxicology information
- Previous human experience
- Additional information

2.2. New drug application (NDA) / Marketing application authorization (MAA)

NDAs (in the U.S.) and MAAs (in the U.K.) are examples of applications to market a new drug. Such application document safety and efficacy of the investigational drug and contain all the information collected during the drug development process. At the conclusion of successful preclinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities in other countries. The application must present substantial evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes between six months and two years [39].

Content and format of NDA [40]:

Two copies of the application are: (1) Archival copy and (2) Review copy.

Archival Copy: It serves as a reference source for FDA reviewers to locate information not contained in the review copy; and it contains copies of tabulations and clinical study case report forms. It contains the following elements:

- Application form FDA 356
- Index
- Summary
- Technical sections: further typed to-
- Chemistry, manufacturing and controls section
- Non-clinical pharmacology and toxicology section
- Human pharmacokinetics and bioavailability section
- Microbiology section
- Clinical data section
- Statistical section
- Pediatric use section
- Samples and labelling
- Case report forms

Review Copy: Each technical section is separately bound in each folder. Each technical section should contain:

- Index
- Copy of FDA Form 356 h
- Copy of cover letter
- Letters of authorization
- Copy of application summary

The FDA can conduct meetings with the sponsor at least two times; once at the end of Phase 2 clinical trials and another before an NDA is submitted i.e., a pre-NDA meeting. The review team shall analyze the study results and make a decision whether

or not to approve the application. The FDA is in continuous interaction with the sponsor throughout the review process [41].

Abbreviated New Drug application (ANDA) [42]:

ANDA is applied for products with same or closely related active ingredients, dosage form, and strength, route of administration, use and labeling as product already shown to be safe and effective. It is used when the patent has expired for a product, and a company wants to market its copy. Such drugs are called generic drugs, which should meet bio and pharmaceutical equivalent standards. An ANDA is submitted to Center for Drug Evaluation and Research, Office of Generic Drugs, where it is reviewed and approved.

Content and format of ANDA [40]:

- Application form
- Table of contents
- Basis for ANDA submission
- Conditions of use
- Active ingredients
- Route of administration, dosage from, strength
- Bioequivalence
- Labeling
- Chemistry, manufacturing and control
- Human pharmacokinetics and bioavailability
- Samples
- Analytical methods
- Case report forms and tabulations.

The Division of Bioequivalence' s Office of Generic Drugs of CDER issued "Guidance on statistical Procedures for Bioequivalence Studies Using a Standard Two Treatment Crossover Design" published in July 1992, which gives regulations on valid statistical analysis for bioequivalence assessment. This ensures the validity of bioequivalence assessment. The FDA has later given a draft guidance entitled "i*n vivo* bioequivalence studies based on population and bioequivalence" that provides recommendations to sponsors of INDs, NDAs, ANDAs, who intend to perform studies based on a comparison of pharmacokinetic metrics [43-45].

All approved drug products, including branded and generic drugs are listed in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations", called ***Orange Book*** [25]. It includes products that are reviewed by FDA for both safety and effectiveness and for which NDAs or ANDAs have been approved. It also provides therapeutic equivalence evaluations for multisource prescription drug products that contain the same active ingredients [44, 46].

Supplemental New Drug Application (SNDA):

After approval of NDA or ANDA, all significant changes in the conditions described in the applications must be approved, by filing a supplemental NDA or ANDA [39]. Such changes like those in packing or ingredients should be approved by the CDER [46]. New-uses approvals of already-approved drugs coming under this category are a better innovation as they need lesser resources to review than that needed for original-use approvals [47].

Drug approval procedure in India

The Drugs and Cosmetics Act 1940 and Rules 1945 were passed to regulate the import, manufacture, distribution and sale of drugs and cosmetics [49]. The drug approval procedure is controlled in India by the Central Drugs Standard Control Organization (CDSCO). CDSCO is headed by the Drugs Controller General of India (DCGI). DCGI works under the Ministry of Health (MOH) and is located in New Delhi [50, 51]. The sponsor should comply with the guidelines and requirements for clinical trials, as provided in the Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945 [52]. An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. The date regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached. Clinical trial on a new drug can be done only after permission by the licensing authority. It is the responsibility of the sponsor to ensure that clinical trials are conducted as per Good Clinical Practices (GCP) [53]. An application on Form 44 for permission of new drugs approval under the provisions of The Drugs and Cosmetics Act 1940 and Rules 1945 should be submitted to the DCGI, which verifies the validity of the application [54].

For an investigational new drug, the sponsor needs to provide detailed information to the DCGI about [50]:

- Generic name
- Patent status
- Brief description of physio-chemical/biological parameters
- Technical information
- Stability
- Specifications
- Manufacturing process
- World-wide regulatory status
- Animal pharmacology and toxicity studies
- Published clinical trial reports
- Proposed protocol and proforma.
- Trial duration
- Drug master file
- Undertaking to report serious or life-threatening adverse drug reactions.

The need for local clinical trials in India depends on the status of drug in other countries. If the drug is already approved in other countries, generally Phase III trials are required. Phase I trials are not allowed in India unless the data is available from other countries. Permission is granted by DCGI to conduct Phase 1 trials in India, if the drug has special relevance to a health problem in India, like malaria or tuberculosis [60, 55]. Bioavailability and bioequivalence (BABE) studies should be conducted as per BABE guidelines. The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy. The information regarding the prescription, samples and testing protocols, product monographs, labels must also be submitted [52]. It usually takes 3 months for clinical trial approval in India [55]. The clinical trials can be registered in the Clinical Trials Registry of India (CTRI), giving details of the clinical trials and the subjects involved in the trials [56].

The rules to be followed under The Drugs and Cosmetics Rules 1945 are [53]:

Rule 122 – A: Application for permission to import new drug.

Rule 122 – B: Application for approval to manufacture new drug other than the drugs specified under Schedule C and C (1).

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

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

Rule 122 - DAB: Compensation in the case of injury or death during the clinical trials [57].

A four year stipulation is given for a 'new drug' from the date of its first approval or its inclusion in the *Indian Pharmacopoeia*, whichever is earlier. After this time period, it can be introduced by obtaining necessary license from the local state Food and Drug Commissioner Office. [50]

Common technical document

Common Technical Document (CTD) is a common format for marketing applications developed in the venue of the International Conference on Harmonization (ICH) [58]. The CTD was made a mandatory format for new drug applications in the EU and Japan in July 2003 [60]. In India, CDSCO adopted CTD format for technical requirements for registration of biological products in the year 2009. CDSCO has given guidelines for feedback purpose for industry on preparation of CTD for import or manufacture and marketing approval of new drug for human use [61, 62].

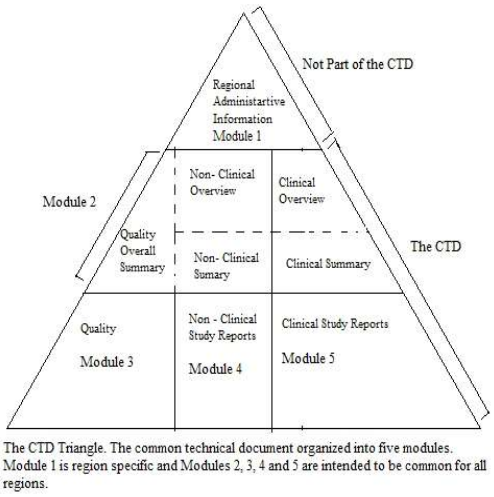
The Electronic Common Technical Document (eCTD) allows for the electronic submission of the Common Technical Document (CTD) and streamlines further the dossier preparation and submission

process, thus saving resources and time. It is based on XML technology, with Document Type Definition (DTD) specification [59. 63, 64]. According to the CTD format, each marketing application should contain 5 modules as listed in the **Table 1**.

Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. The CTD triangle is illustrated in **Figure 3** [60].

Table 1: Modules of CTD [59]

MODULE	INFORMATION
1	Administrative and prescribing information
2	Summaries and overview
3	Information on product quality
4	Non-clinical study reports
5	Clinical study reports



The CTD Triangle. The common technical document organized into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions.

Figure 3: The CTD triangle [35]

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 wellbeing 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 .[65] The Department of Chemical and Petrochemicals of Ministry of Chemicals and Fertilizers, through National Pharmaceutical Pricing Authority (NPPA) [66] 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.

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 Fertilizers 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 .[67] 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. [68]

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 [68]. These zonal offices work in close collaboration with the state offices to bring about uniform enforcement of the regulations imposed by the central government.

Some of the important rules that regulate clinical trials in India include:

a) Schedule Y of Drugs and Cosmetic Act and Rules (Amended in 2005) [70]. These are the requirements and guidelines for permissions to import and manufacture new drugs for sale or to undertake clinical trials.

b) GCP guidelines issued by CDSCO in 2001 [71]. These guidelines specify ―the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. They ensure safety and well-being of subjects and verify the authenticity of the data being generated. They must be followed at all stages of drug development.

c) Ethical guidelines for Biomedical Research on Human Subjects by ICMR (amended in 2006) [71]: They lay down the principles of essentiality, voluntariness, nonexploitation, privacy and confidentiality of subjects.

Recent amendments in Schedule Y

a) Introduction of Rule 122DAB (also called as the Drug and Cosmetics Act (First Amendment) and Appendix XII: This rule provides directives about compensation for injury and death during the clinical trials. It states that a subject is entitled to compensation injury and death during the clinical trials. It states that a subject is entitled to compensation if injury or death is due to:

1. Adverse effect of investigational product (s) (IP);
2. Violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator;
3. Failure of IP to provide intended therapeutic effect;
4. Use of placebo in a placebo-controlled trial;
5. Adverse effects due to concomitant medication excluding standard care, caused as part of approved protocol;
6. For injury to a child in-utero because of

the participation of parent in a clinical trial;
7. Any clinical trial procedures involved in the study. [72]

(b) Introduction of Rule 122DAC (Second Amendment): This rule specifies various conditions for conduct and inspection of clinical trials. It specifies the prerequisites required for a clinical trial to be considered as adequate, in order for the Licensing Authority to grant permission for conduct of the trial on humans. Further, the rule lays down the power of the Licensing Authority to impose any other conditions to be fulfilled in case of grant of permission to a clinical trial, as considered fit.

c) Insertion of Rule 122 DD (Third Amendment): It deals with mandatory registration of the Ethics Committee and specifies that no Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of rule 21 and describes the procedure of such registration to be made by filling an application directed to the Licensing Authority as per the requirements specified in the Appendix VIII of Schedule Y of the Rule and the procedure thereof [73].

Ethical consideration [35]

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 investigators 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.

Informed consent

Proper informed consent is essential. Partly as a result of terrible things done in the name of clinical research, various bodies developed guidelines such as the Nuremberg Code [74], the Declaration of Helsinki [75], the Belmont Report [76], and the International Ethical Guidelines for Biomedical Research Involving Human Subjects [77]. These guidelines lay out standards for informed consent that are commonly followed internationally. In the USA, in parallel to the Belmont Report, the United States Congress passed laws that require adherence to informed consent

regulations by those receiving government support – the so-called Common Rule, or 45 CFR 46 [78] – and those evaluating agents under the auspices of the Food and Drug Administration [79]. These regulations require that clinical research studies be reviewed by IRBs and establish the membership and procedures that IRBs must follow.

One of the primary roles of the IRB is to ensure that there is true, voluntary informed consent. The Common Rule requires consent forms to contain basic elements. Other elements that may be added as appropriate. Simply adhering to legal requirements does not ensure informed consent [80-82]. Informed consent is a process that can take considerable time and effort; it is not simply a matter of getting a form signed. In many, perhaps most, clinical trial settings, true informed consent can be obtained. Potential participants have the capacity to understand what is being requested of them, they have adequate time to consider the implications of joining a trial, to ask questions, and to take information home to review and discuss with their families and personal physicians, and they are familiar with the concepts of research and voluntary consent.

Safety and efficacy monitoring

Occasionally, during a trial, important information relevant to informed consent derives either from other studies or from the trial being conducted. In such cases, the investigator is obligated to update the consent form and notify current participants in an appropriate manner. A trial of antioxidants in Finnish male smokers (the Alpha-Tocopherol Beta Carotene Prevention Study) indicated that beta carotene and vitamin E may have been harmful with respect to cancer or cardiovascular diseases, rather than beneficial [83]. Because of those findings, investigators of the ongoing Carotene and Retinol Efficacy Trial (CARET) informed the participants of the results and the possible risks [84]. CARET was subsequently stopped earlier than planned because of adverse events similar to those seen in the Finnish trial. The investigator of a third trial of antioxidants, the Age-Related Eye Disease Study (AREDS) then notified their participants of the findings from both the Finnish study and CARET [85, 86].

Randomized control trial

Randomized controlled trial (RCT) is defined as a study in which people are allocated at random to receive one of several clinical interventions. One of these interventions is the standard of comparison or control. The control may be a standard practice, a placebo, or no intervention at all. RCTs seek to measure and compare the outcomes after the participants receive the interventions. Because the outcomes are

measured, RCTs are quantitative studies [87].

Following implementation of the product patent in India, almost all multinational companies started large RCTs here. The main attractions were a 50% drop in operational cost, low per patient trial cost, large number of qualified English speaking professionals, large patient pool with diverse ethnicity, extensive network of hospitals and laboratories, good communications with information technology and above all, easy and fast recruitment of patients [88].

The path was smooth until 2011 when a dramatic drop in conducting and delivering the international RCTs outsourced to India was noticed. According to certain calculations, this drop is up to 50%. [89] At the same time international outsourcing of RCTs to China, Russia and Philippines has increased. In a pursuit to find an answer to this drastic decline-the conduct of trials, ethics, regulatory environment and the quality of data – all are challenged.

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