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A review on drug approval process in US, Europe and India-dossier, bioavailability and bioequivalence studies

Dr. krishna Madagoni[1]*, Uppunuri Saidireddy[1], Himaja[2]

1. Department of Quality Assurance, InvaGen pharmaceutical Inc.
2. Department of Pharm.D, K.V.K College of Pharmacy, JNTUH, Telangana, India.

Corresponding author: Dr. Krishna Madagoni
Email address: pharmarxpro@gmail.com

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ABSTRACT:

Pharmaceutical Regulatory Affairs (PRA) is a vital unit in a pharmaceutical company that successfully drives the Research and Development (R&D) efforts of the company to the market. In the present scenario, countries have different regulatory requirements for approval of a new drug. The single regulatory approach for marketing authorization application (MAA) of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for MAA of each country should be known to establish a suitable regulatory strategy. CTD was developed with the aim to provide a common format for the technical documentation that would significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and would ease the preparation of electronic submissions. Bioavailability and bioequivalence testing are essential in the drug development process as they create the foundation for regulatory decision making when evaluating formulation changes and lot-to-lot consistency in innovator products. They also serve as the primary components to demonstrate therapeutic equivalence between generic products and the reference innovator product. This article will focus the similarities and differences in drug approval process & requirements of the documents/CTD specifications to the drug regulatory authorities in the Europe, USA and India also focuses on submission and work flow related to bioavailability and bioequivalence studies.

Introduction

Drug development is long, risky, expensive process and these characteristics mean regulatory affairs has forceful emphasis to improve safety, efficacy and quality of the medicinal product (Monappa R Sutra et al., (2013). In the present scenario, countries have different regulatory requirements for approval of a new drug. The single regulatory approach for marketing authorization application (MAA) of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for MAA of each country should be known to establish a suitable regulatory strategy (Prajapati Vishal et al., 2014). The regulatory affairs authorities are the only one who is completely responsible for holding products in compliance and maintaining all the records. Drug development for commercialization is highly regulated; every drug before getting market approval must undergo rigorous scrutiny and clinical trials to ensure its safety, efficacy and quality. These standards are set by regulatory authorities of their respective countries such as FDA in US and DCA in India etc. In 2000, representatives from the European Medicines Agency (EMA), the USA FDA, and the Ministry of Health, Labour, and Welfare in Japan developed a set of guidelines defining the structure and content of the dossier for an application for the registration of a new medicine that could be used across all three regions. These guidelines were developed under the umbrella of The International Conference on Harmonisation (ICH) and have become part of the family of ICH guidelines. The aim of the CTD was simple – it would provide a common format for the technical documentation that would significantly reduce the time and resources needed

to compile applications for registration of human pharmaceuticals and would ease the preparation of electronic submissions (Jordan et al., 2014). Pharmaceutical companies are now a days immensely competitive and are spending billions of rupees in the new drug development process. However, the success rate is very less. Therefore, most of the companies are in conquest of the generic market; Generics are not required to repeat the extensive clinical trials used in the development of the original, brand-name drug. Instead, generics must show they are bioequivalent to the pioneer (Innovator product) drug and fall into acceptable parameters for bioavailability, or the extent and rate at which the body absorbs the drug (Arora Tarun et al., 2011).

Figure 1: The following figure shows the regulatory bodies as per the country.

Regulatory affairs take care of development plan, supervising-writing / reviewing and assembling and submission management. They give strategic and technical advice at the highest level in their companies, right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development programme and the company as a whole (Monappa R Sutra et al., 2013). So, this paper reviews here for the comparative drug approval process, common technical document (CTD), bioavailability and bioequivalence studies.

Regulatory affair profession and its need

The (Healthcare) regulatory affairs profession is still an emergent profession but has two major international professional membership societies. The Regulatory Affairs Professionals Society (RAPS), Organization for Professionals in Regulatory Affairs (TOPRA). In Canada, the major professional membership society is: The Canadian Association of Professional Regulatory Affairs, CAPRA. In today's competitive environment the reduction of the time taken to reach the market is vital to a product's and hence the company's success. The proper conduct of its regulatory affairs activities is therefore of considerable economic significance for the company. Inadequate reporting of data may prevent a timely positive evaluation of a marketing application. A good regulatory affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific endeavour with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources.

The regulatory affairs department is very often the first point of contact between the government authorities and the company. Officials respond much better to a company whose representatives are scientifically accurate and knowledgeable than to one in which these qualities are absent (Monappa R. Sutra et al., 2013).

Mode of regulatory submission

There are different guidelines to approach to the regulatory bodies for getting marketing authorization for the pharmaceutical products in different countries in the world. But by initiations by European regulatory body with the conjunction of USA and Japan, have approached the common document called CTD dossier for the documentary submission. For the drug approval process various countries having different but specific approach for the approval. Some of the common approval processes are described as per the regulatory authority (Jordan et al., 2014).

Regulatory approval & submission procedure in USA

The Food and Drug Administration is responsible for protecting and promoting public health. Like general drug approval process, FDA's new drug approval process is also accomplished in two phases: clinical trials (CT) and new drug application (NDA) approval. FDA approval process begins only after submission of investigational new drug (IND) application. The IND application should provide high quality preclinical data to justify the testing of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. The next step is phase I, phase II and phase III clinical trials. A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labeling. The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Center for Drug Evaluation and Research by a team of scientists. Generally approval of an NDA is granted within two years (on an average), however, this process can be completed from two months to several years. The innovating company is allowed to market the drug after the approval of an NDA and is considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants

respond to different dosages are explored. Figure 2 represents the new drug approval process of FDA.

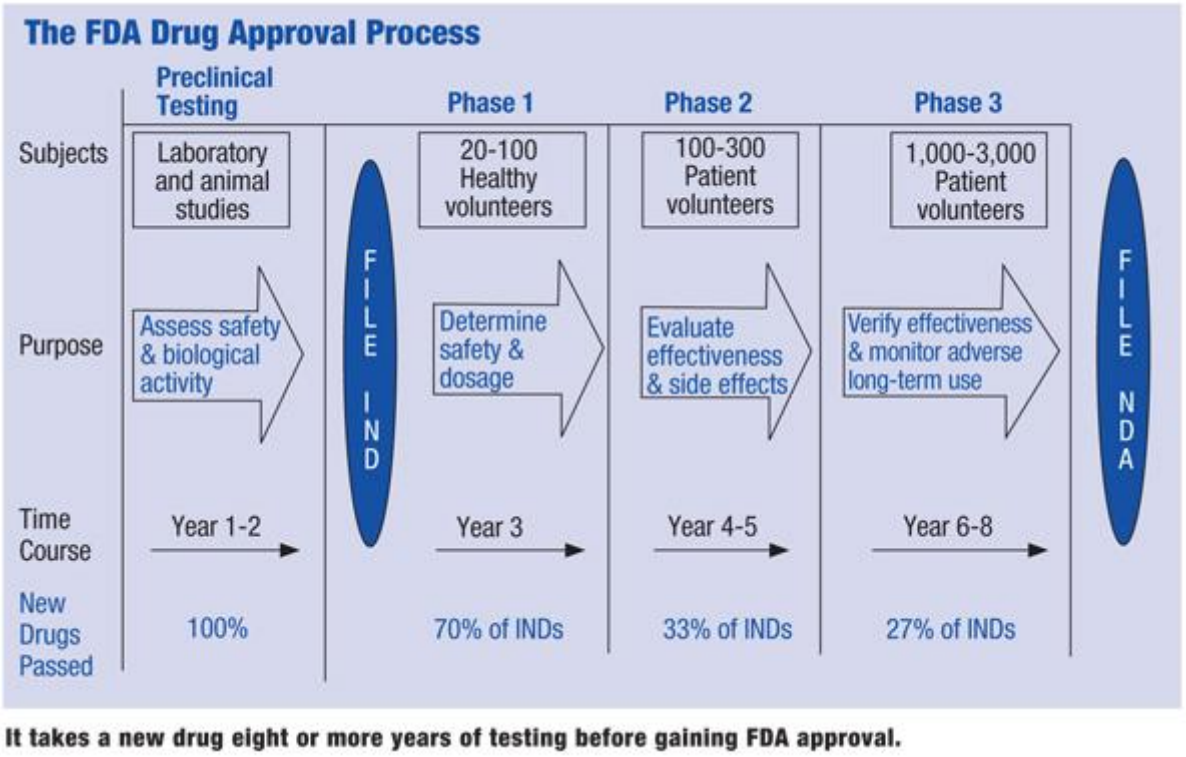

Figure 2: The new drug approval process of FDA (Martis S Lipsky et al., 2001)

The initial phase in the FDA approval process is pre-clinical phase. In the pre-clinical or drug discovery phase of the approval process, researchers look for potential new compounds to treat targeted diseases. Once a compound has been identified and refined to a formula that can be tolerated by humans, its toxicology is tested in animals and living tissue. The process takes roughly three and a half years. During this phase researchers look for

- How frequently it should be administered
- Best delivery system (oral, topical, intravenous, etc.)
- Short- and long-term survival of the animals

After pre-clinical testing is completed, the company then files an Investigational New Drug Application (IND) with the FDA. Fast Track Designation is an expedited review of a drug that is given to a company whose drug or biologic makes both a product and a marketing claim that addresses an unmet medical need. It can be granted at any point after the FDA approves an IND.

Phase I: If the FDA approves the IND, the experimental drug then moves into Phase I human testing. In this phase, the drug is tested in a small number (under 100) of healthy participants. Researchers look to see how well the drug is tolerated, how it is processed by the human body, and the correct dosing. This process takes a year.

Phase II: Once a compound is found to be well tolerated in healthy individuals, it is then tested for effectiveness for a targeted disease in a small number of patients. In this phase 100-300 people are administered the investigational drug to see if it actually works, and to determine its short-term effects. This process takes about two years.

Phase III: Phase III is a large-scale study of the effectiveness and side effects of the drug in a larger population, usually ranging from 1000-3000 patients. If the drug is submitted to the FDA for approval, the FDA will look at the Phase III data to determine if the drug is safe and effective. Aside from testing the drug's viability, the company producing the drug also determines the logistics involved in creating a large supply of the treatment. Phase III of the FDA approval process takes about three years. New Drug Application (NDA)/ Biologics License Application (BLA) can be filed with the FDA if the drug proves to be safe and effective. NDAs and BLAs are typically 100,000 pages long and include results of human and animal trials as well as information on how the drug is manufactured. It usually takes the FDA 1-2 years to complete the review process and approve a drug. However, there are cases when approval can be accelerated.

At the time of application Priority Review can be granted to drugs that treat an unmet medical need. Orphan Drug Status is granted to drugs that treat rare diseases, or diseases that have no other available treatments.

Phase IV: Once a drug has received FDA approval it is then marketed to the general population. Short and long-

term side effects continue to be monitored and results are submitted to the FDA. Companies will also look for additional indication for the drug. In order for the drug to be approved for a new indication, it must receive approval from the FDA.

Abbreviated New Drug Application (ANDA) It's an application made for approval of Generic Drugs. The sponsor is not required to reproduce the clinical studies that were done for the original, brand name product. Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product (U. Nitin Kashyap et al., 2013, Monappa R Sutra et al., 2013, Mulaje et al., 2013).

Regulatory approval & submission procedure in Europe (EU)

Pharmaceutical companies of EU use three approval procedures to market their pharmaceuticals
1) Centralized
2) Decentralized
3) Mutual recognition procedure

1. Centralised Procedure:

Which is compulsory for products derived from biotechnology, for orphan medicinal products and for medicinal products for human use which contain an active substance authorised in the Community after 20 May 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes. The centralised procedure is also mandatory for veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth or to increase yields from treated animals. Applications for the centralised procedure are made directly to the European Medicines Agency (EMA).

Centralized procedure allows a pharmaceutical company to market its pharmaceutical product in all 25 member states, without having to obtain separate approvals from each member state. Applications through the centralized procedure are submitted directly to the agency. Evaluation by agencies scientific committees takes up to 210 days, at the end of which the committee adopts an opinion on whether the medicine should be marketed or not. This opinion is then transmitted to the European commission, which has the ultimate authority for granting marketing authorization in the EU. After the marketing authorization has granted, the marketing authorization holder can begin to make the medicine available to the patients and healthcare professional in the EU countries. Figure 2 illustrates the centralised procedure to get approvals in Europe.

2. Mutual recognition procedure:

Applicable to the majority of conventional medicinal products, is based on the principle of recognition of an already existing national marketing authorisation by one or more Member States.

The Mutual Recognition procedure allows applicants to obtain a marketing authorization in the Concerned member states (CMS) other than the Reference member state (RMS), where the drug is previously approved. The applicant submits identical dossier to all EU member states in which they want marketing authorization, including required information.

- As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "RMS"), it notifies this decision to other Member States (which then become the "CMS"), to whom applications have also been submitted.
- RMS issues a report to other states on its own findings.
- Generic industry is the major user of this type of drug approval procedure.

This process may consume a time period of 390 days.

3. Nationalized Procedure

The Nationalized procedure is one which allows applicants to obtain a marketing
authorization in one member state only.

- In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.
- New active substances which are not mandatory under Centralized procedure can obtain marketing authorization under this procedure.
- Timeline for this procedure is 210 Days.

4. Decentralized procedure

Using this procedure, companies may apply for authorization simultaneously in more than one EU country for products that have not yet been authorized in any EU country and essentially do not fall within the centralized procedure's essential drugs list. Based on the assessment report which is prepared by the RMS & any comments made by the CMS, marketing authorization should be granted in accordance with the decision taken by the RMS & CMS in this decentralized procedure.

- Generally used for those products that has not yet received any authorization in an EU country.
- Time: 210 days (Vishal et al., 2014, Pratik Makvana et al., 2014).

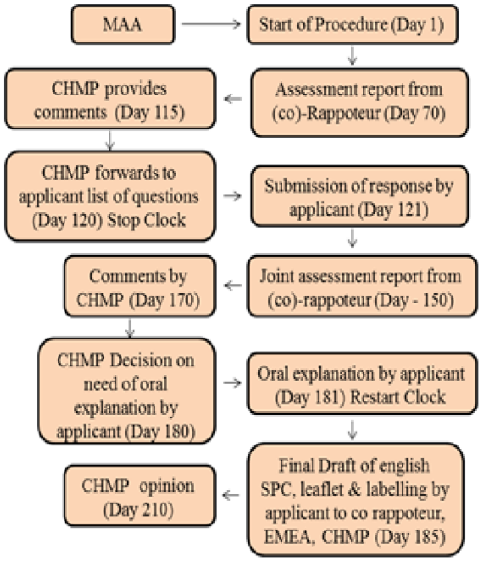

Figure 3: Flow chart of centralised procedure

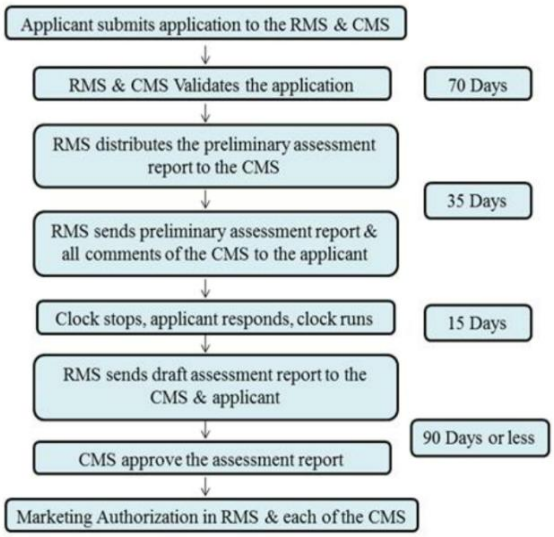

Figure 4: Flow chart of decentralised procedure

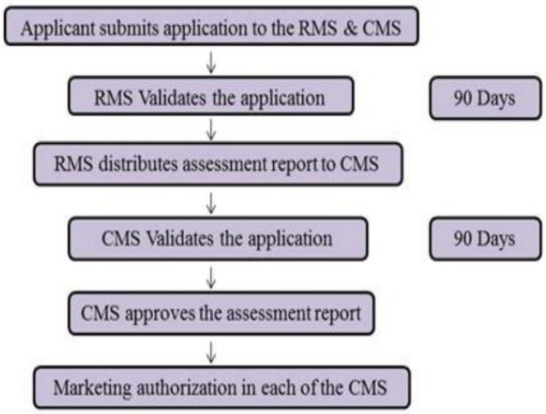

Figure 5: Flow chart of mutual recognition procedure

Regulatory approval & submission procedure in India

New Drug Approval

The new drug approval process in India is standardized and well controlled, involving multiple steps and organizations. At the central level, DCGI, under the Ministry of Health and Family Welfare, approves the drug or medical device for marketing. Manufacturing licenses are approved at the state level by state drug control authorities. Monitoring is also performed by state agencies in coordination with the CDSCO.

Manufacturing, importing, or conducting a clinical trial requires permission from the licensing authority through a Form 44 application. The application follows international submission requirements of a Common Technical Document (CTD) and has five modules.

Form 44 requires information as described in Schedule Y of the Drugs and Cosmetics Act. The clinical trial must be conducted in accordance with ethical principles. The Act has a special provision (Rule 122-A) to accept international trial data or other information, to allow import, and to waive the clinical trial requirement in the interest of public health. A clinical trial may also be waived for drugs that are approved and have been used in other countries for many years. Appendix I, IA, and VI of Schedule Y describe the information and data required for approval of clinical trial and/or import or manufacture of a new drug for marketing in the country. However, requirements for approval of clinical trials and new drugs may vary depending on the nature of the new drugs.

The application for permission seeks detailed information including:

- Chemical and pharmaceutical information,
- Animal pharmacology data,
- Animal toxicology data,
- Human clinical pharmacology data,
- Regulatory status in other countries,
- Full prescribing information as part of new drug approval for marketing,
- Complete testing protocols for quality control testing, and
- Complete impurity profile and release specifications for the product.

Clinical Trial Process

The structure and nature of the clinical trial process in India is exactly the same as those mandated by major regulatory agencies around the world. Clinical trials are permitted after submission of animal data studies and

other pharmacological data, and after receiving Investigational New Drug Application approval.

The clinical trials were further divided into two categories in 2006. In one category (category A) clinical trials can be conducted in other markets with competent and mature regulatory systems whereas the remaining ones fall in to another category (category B) other than A. Clinical trials of category A (approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for fast tracking in India, and are likely to be approved within eight weeks. The clinical trials of category B are under more scrutiny, and approve within 16 to 18 weeks. 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. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee. To determine the maximum tolerated dose in humans, adverse reactions, etc. on healthy human volunteers, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level. The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3- 4 centres) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centres, if the new drug substance is not marketed in any other country. The new drug registration (using form number 44 along with full preclinical and clinical testing information) is applied after the completion of clinical trials. 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 monograph, labels, and cartons must also be submitted. The application can be reviewed in a range of about 12-18 months. Figure 2 represents the new drug approval process of India. After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials, in which new uses or new populations, long-term effects, etc. are explored. The drug approval process varies from one country to another. In some countries, only a single body regulates the drugs and responsible for all regulatory task such as approval of new drugs, providing license for manufacturing and inspection of manufacturing plants e.g. in USA, FDA performs all the functions. However in some counties all tasks are not performed by a single regulatory authority, such as in India, this responsibility is divided on Centralized and State authorities. Other issues where the difference appears are, time taken for the approval of a Clinical Trial Application (CTA), time taken in evaluation of marketing authorization application, registration fee, registration process and marketing exclusivity. Some counties have two review processes as normal review process and accelerated review process as in USA, China etc. and some countries have only a single review process as in India. Similarly, the format used for the presentation of dossier submitted for approval of drug is also different. In some countries like in USA, EU, and Japan, it is mandatory that the dossier prepared in CTD format, however, in some countries it is optional such as in India. Once the drug is approved for clinical usage, safety surveillance is mandatory to study the long-term side effects.

ICMR maintains Clinical Trial Registry-India (CTRI), a free online public record system for registration of clinical trials designed to track all ongoing trials (Ramu et al., 2015).

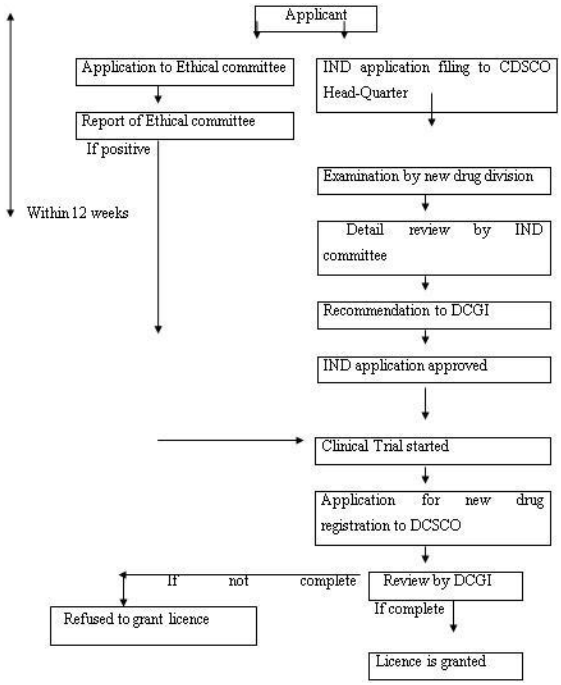

Figure 6: Flow Chart for the Drug Approval process in India

Common technical documents (DOSSIER)

Dossier is a file document submitted for the approval of new drug or drug product. CTD is a harmonized format (template) for presenting data in the ICH regions. In some country it is optional.

The aim of the CTD was simple – it would provide a common format for the technical documentation that would significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and would ease the preparation of electronic submissions. In addition, regulatory reviews and communication with the applicant would be facilitated by a standard document of common elements and the exchange of regulatory information between

Regulatory Authorities would be simplified.1 The CTD dossier is divided into five main modules (see Figure 7):
Module 1: Administrative information and prescribing information
Module 2: Overviews and Summaries of Modules 3–5
Module 3: Quality (pharmaceutical documentation)
Module 4: Non-clinical reports (pharmacology/toxicology)
Module 5: Clinical study reports (clinical trials).
Module 1 is not strictly included in the CTD since it contains documents that are specific to each region, e.g. application forms or the proposed label. This module will not be discussed in any further detail in this article since the content and format of this module is specific to individual Regulatory Authorities.
Modules 2–5 though are common to all regions and these comprise the main body of the CTD.
Module 2 contains the CTD overviews and summaries. It starts with a general introduction to the drug, including its pharmacological class, mode of action, and proposed clinical use. Module 2 then provides an overall summary of the 'quality' information (i.e. the pharmaceutical documentation), as well as the Non-Clinical Overview and the Clinical Overview, the Non-Clinical Written Summaries and the tabulated summaries, and the Clinical Summary. The information provided in Module 2 is based on the foundation material that is provided in Module 3 for the quality information, Module 4 for the non-clinical information, and Module 5 for the clinical information.

The process of reviewing & assessing dossier to support a medicinal product in view of its marketing (also called licensing, registration, approval, etc.), is finalized by granting of a document also called marketing authorization. This process is performed within a legislative framework which defines the requirements necessary for application to the concerned (competent) regulatory authority, details on the assessment procedure (based on quality, efficacy and safety criteria) and the grounds for approval or rejection of the application, and also the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked. The application dossier for marketing authorization is called New Drug Application (NDA) in the USA or Marketing Authorization Application (MAA) in the European Union and other countries, or simply registration dossier. Basically, this consists of a dossier with data proving that the drug has quality, efficacy and safety properties suitable for the intended use, additional administrative documents, samples of finished product or related substances and reagents necessary to perform analyzes of finished product as described in that dossier. The content and format of the dossier must follow rules as defined by the competent authorities. For example, since year 2003, the authorities in the United States, the European Union and Japan ask for the Common Technical Document (CTD) format, and more recently, its electronic version - the electronic Common Technical Document (eCTD). The application is filed with the competent drug regulatory authority in the concerned country, which can be either an independent regulatory body or a specialized department in the ministry of health. In accordance with local legislation, the resulting document allowing to the applicant to market the product may be more detailed (in addition to data identifying the product and its holder it may contain addresses of all manufacturing sites, appended labeling, artwork of packaging components, etc.) until a one-page document called certificate of registration (and containing minimal data identifying the product and its source).

Generic drug: A generic drug is a drug defined as "a drug product that is comparable to brand/reference listed drug (RLD) product in dosage form, strength, route of administration, quality and performance characteristics, and intended use." It has also been defined as a term referring to any drug marketed under its chemical name without advertising. According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetic and pharmacodynamic properties. By extension, therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use.

The FDA's use of the word "identical" is very much a legal interpretation, and is not literal. In most cases, generic products are available once the patent protections afforded to the original developer have expired.

The generic drug products marketing authorizations are also seeks the CTD formats. Approved under ANDA submission (USA) MAA submission (EU) Generic drug applications are termed as "Abbreviated". RLD - An approved drug product to which new generic versions are compared to show that they are bioequivalent. Orange book - Approved drug product with therapeutic equivalence evaluations, published by the FDA (CDER). Hatch-Waxman act 1984 eliminates the costly clinical trial for approval of generic drugs. CDSCO is regulatory authority for the approval of new drugs proposed to be imported. (India). CTD format intends to harmonize the structure and format of registration documentation. Benefits Complete, well-organized submissions, facilitates electronic submissions, easier analysis across applications etc. (Mimansha Patel et al., 2013, Jordan et al., 2014).

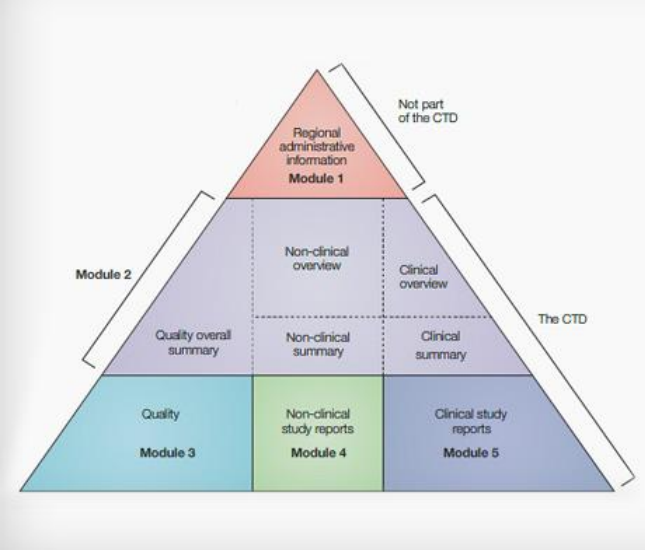

Figure 7: CTD Triangle (Pratik Makvana et al., 2014)

The CTD is organized into five modules:

Table 2: Differences between US, European and Indian submissions

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.Centalized (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 application): € 103,059 Decentralised procedure where UK is CMS:€ 99,507**	**50,000 INR**

Regulatory guidelines for dossier submission in India

The following regulatory authorities run in India for the drug discovery, development and approval process. CDSCO: A licensing authority for approval of new drug proposed to be imported Head office located in New Delhi & functioning under the control of directorate general of Health services, MHFW, Govt of India. 29 DCGI: Responsible for approval of new drug & Clinical trials to be conducted in India Appointed by Central Govt. of India. Drug & Cosmetic Act 1940 & Rules

1945: Regulates the import, manufacture, distribution & sale of drugs & cosmetics. Schedule Y: Provides guidelines & requirements for clinical trials (Mimansha Patel et al., 2013).

Comparative study of dossier submission process of drug product in USA, EU, India.

Submission related to the Administrative The following requirements to be submitted for the regulatory bodies for granting market authorization. For the European country the application for the new drug product is submitted to marketing authorization application agency. As per the country guideline there is no need to submit patent status or debarment certificate. The document should be submitted in the eCTD format, in 1 sets. Generally it takes 12 to 18 months for the approval. There is a submission fee for approval i.e. 10 to 20 lakh. Major hold up during authorization is patent infringement, GMP audit, high cost of registration, administrative procedure for each member state. For the country United States of America the application for the new drug product is submitted as New Drug Application (NDA) and for the generic drugs application should be submitted as Abbreviated new Drug Application (ANDA) along with the patent status or debarment certificate. The document should be submitted in the eCTD format or paper, in 3 sets. Generally it takes 12 to 24 months for the approval. There is no any fee for the submission. Major hold up during authorization is patent infringement, FDA audit, competition. For India the application for the new drug product (IND) is submitted to CDSCO Delhi. As per the country guideline there is no need to submit patent status or debarment certificate. The document should be submitted in the CTD paper format, in 1 sets. Generally it takes 12 months for the approval. There submission fees for approval is 50 thousands. Major hold up during authorization is obtaining certificate for pharmaceutical product (CPP) may delay the process and administrative procedure in individual countries which leads time delay in approval (Swapna G et al., 2014, Monappa R. Sutra et al., 2013).

Submission & work flow related to bioavailability and bioequivalence study

Bioavailability (BA) and bioequivalence (BE) testing are essential in the drug development process because they create the foundation for regulatory decision making when evaluating formulation changes and lot-to-lot consistency in innovator products. They also serve as the primary components to demonstrate therapeutic equivalence between generic products and the reference innovator product. The increasing number of drugs that can be obtained from different manufacturers and the phenomenal growth of the generic pharmaceutical industry have prompted regulatory agencies such as Food and Drug Administration (FDA) to establish BA and BE regulations put into effect in January 1977. BA studies are performed for both approved active drug ingredients and therapeutic moieties not yet approved for marketing by the FDA. New formulations of active drug ingredients must be approved by the FDA before marketing. In approving a drug product for marketing, the FDA ensures that the drug product is safe and effective for its labeled indications for use. Moreover, the drug product must meet all applicable standards of identity, strength, quality, and purity. To ensure that these standards are met, the FDA requires BA/pharmacokinetic studies and, where necessary, BE studies for all drug products. For new drugs not fully approved for marketing, regulatory agencies require that *in vivo* BA studies should be performed on the dosage form proposed for marketing. *In vivo* BA studies are also performed for new formulations of active drug ingredients or therapeutic moieties that have full NDA approval and are approved for marketing.

Table 3: Comparison of some bioequivalence guidelines of US, Europe and India (CDSCO),

S.No	Criteria	FDA	EMA	CDSCO
1.	General	Single dose, non-replicate cross-over study for immediate release and modified release dosage forms and a single-dose, two-period, two-treatment, two-sequence cross study designs for fed BE studies	Single dose, randomized, 2-Period, 2 Sequence cross over design.	Single dose, randomized, 2 -Period, 2-treatment, cross-over study design.
2.	Long half-	Non replicate single	Parallel design for	Parallel design for

	Life drugs/highly variable drugs	dose crossover with Adequate washout period /parallel study design.	long half-life drug and replicate for highly variable drugs.	long half-life drugs and replicate designs for drugs with variable disposition.
3.	Number of subjects	Healthy Volunteers, minimum number of volunteers to be taken in the study should be 12.	Healthy Volunteers, Minimum number of volunteers should not be less than 12 unless justified.	Healthy Volunteers, Not less than 16 unless justifi ed for ethical reasons
4.	Replacement of subjects on withdrawal or dropout	Not specified.	The data from all treated subjects should be included in the study. There is no such thing as 'spare' subjects in the study.	Acceptable to replace a subject withdrawn/drop -out from the study once the study has begun provided the substitute follows the same protocol originally inten ded for the withdrawn subject and the subject is tested under similar controlled conditions.
5.	Strength of the dosage form	In most of the cases, the highest strength.	For drugs with Linear pharmacokinetics, use of highest strength is preferred. For drugs with non-linear pharmacokinetics, the establishment of BE studies both at the highest and at the lower strength is required.	Not specified.
6.	Single/ Multiple dose	Single dose studies are preferred for Both immediate and modified release drug products. Multiple dose studies are conducted only wherever required.	Multiple dose studies are acceptable only in cases where it not possible to carry out single dose studies.	Single dose studies are preferred except for some special situations, where the conduct of steady state studies are acceptable.

7.	Fasting prior to study	10h before and 4h after drug administration.	8h before and 4h after the administration of product, unless otherwise justified.	Single dose: At least 10h Overnight and 4 h after dosing. Multiple dose: 2 h before and after dose.
8.	Food Specification for "fed Studies"	A high-fat (approximately 50 percent of total caloric content of the meal) and high -calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for "Food -effect BA" and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.	High fat (approx. 50% of total caloric content of the meal) and high calorie (approx. 800-1000 kcal) meal.	Requires consumption of a high-fat breakfast approx. 15 min. before dosing (950-1000KCalories) {50% of Calories should be derived from fats, 15-20% of Calories from proteins and Rest Carbohydrates}.
9.	Fluid (water) intake	Drug should be administered with 8 ounces (240 ml) of water under fasting conditions. The subjects should not be allowed to consume water 1h before and after the drug administration.	Drug should be administered with standard volume of fluid, at least 150 ml. Subjects are not recommended to consume water 1 h before and after the drug administration.	Drug should be administered with standard quantity of fluid.
10.	Sampling	12-18 samples including the pre-dose sample per dose per subject should be collected. Sampling should be distributed once three or more terminal half-lives of the drug.	Measurements should be taken to avoid Cmax being the first point of concentration time cure. At least 2-4 samples needed during the terminal log-linear phase.	At least 3 sampling points during the absorption phase, 3-4 at projected Tmax and 4 points during the elimination phase.
11.	Wash-out period	More than 5 half-lives of the moieties	For Steady State; at least 5 times the	Not specified.

		to be measured.	terminal half -Life.	
12.	Parameters	AUC 0-t, AUC 0-∞, Cmax, Tmax, t1/2 Steady State: Cmin, Cav, degree of fluctuation and swing.	AUC 0-t, AUC 0-∞, tmax, Cmax, residual area Steady State: AUC 0-τ, Cmax, ss, Tmax, ss	AUC 0-t, AUC 0-∞, AUC 0-τ, Cmax, Kel Steady State: AUC 0-τ (ss) , Cmax, Cmin, Cpd and deg. of fluctuation.
13.	Acceptance criteria	90% confidence interval between 80-125%. It recommends additional tests and/or controls to ensure the quality of drug products containing Narrow Therapeutic Range Drugs.	90% confidence interval between 80-125%. AUC should be tightened to 90-111.11% for narrow therapeutic range drugs and 69.84%-143. 19% for highly variable drugs.	90% confidence Interval between 80-125%. No specifications on narrow therapeutic drugs.

Bioavailability is a measurement of the extent of a therapeutically active medicine that reaches the systemic circulation and is therefore available at the site of action. For most medicines that are taken orally, the active ingredients are released in the gastrointestinal (GI) tract and arrive at their site of action via the systemic circulation. Blood concentrations of the active ingredients and/or their active metabolites thereby provide a marker for the concentration at the site of action and a valid measure of bioavailability. A blood concentration – time curve (achieved by serial measurements over time) reflects not just the release of the active ingredient from the medicine and its absorption from the GI tract, but also other factors including presystemic metabolism, distribution and elimination. Bioavailability is assessed using three main pharmacokinetic variables. Area under the blood drug concentration versus time curve (AUC) Maximum blood concentration (Cmax) Time to reach maximum concentration (Tmax) Bioavailability example A hypothetical drug given orally has a bioavailability of 50% (or 0.5), this is due to: 1. Incomplete absorption in the GI tract so that only 70% of the initial dose is absorbed. 2. Subsequent metabolism of a further 20% before it reaches the systemic circulation (e.g. first pass through the liver). Therefore only 50% of the original oral dose reaches the systemic circulation.

Bioequivalence If two medicines are bioequivalent there is no clinically significant difference in their bioavailability. Although bioequivalence is most commonly discussed in relation to generic medicines, it is important to note that bioequivalence studies are also performed for innovator medicines in some situations such as:

A. Between early and late clinical trial formulations or between the formulations used in clinical trials and the product to be marketed for new medicines
B. When changes in formulation have occurred after an innovator product has been approved, for example a change in one or more excipients (inactive ingredients).

Bioequivalence studies are a surrogate marker for clinical effectiveness and safety data as it would not normally be practical to repeat clinical studies for generic products. It is accepted that if plasma concentrations of the active ingredient of the generic and innovator medicines are the same, then their concentration at the site of action and therefore their safety and effectiveness will be the same. In addition to being bioequivalent, a generic medicine must conform to high quality standards in terms of the method of manufacture and the purity of the final pharmaceutical form. There are international standards for measuring and assessing bioequivalence.

Acceptance Criteria for Bioequivalence

Bioequivalence is determined based on the relative bioavailability of the innovator medicine versus the generic medicine. It is measured by comparing the ratio of the pharmacokinetic variables for the innovator versus

the generic medicine where equality is 1. The acceptance criteria are such that to be classified as bioequivalent, plasma concentrations of the generic medicine will not differ significantly compared with the innovator medicine. Studies have demonstrated that actual differences between observed mean plasma concentrations of generic and innovator medicines were no greater than 5%. In order to determine that two medicines are bioequivalent there must be no more than a 20% difference between the AUC and Cmax. This is based on international consensus that differences less than this are not clinically significant. In order to establish this, the AUC and Cmax for the generic medicine are compared to that for the innovator medicine (Nitika Kaushal et al., 2016).

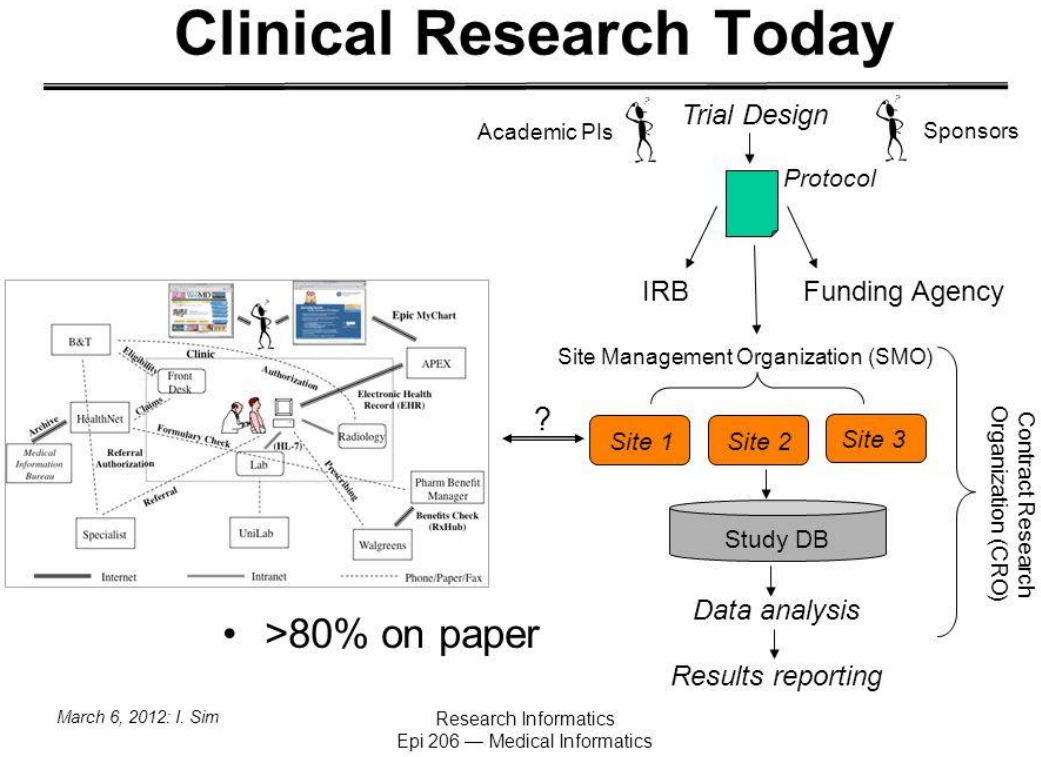

Figure 8. General Flow of Study at the CRO

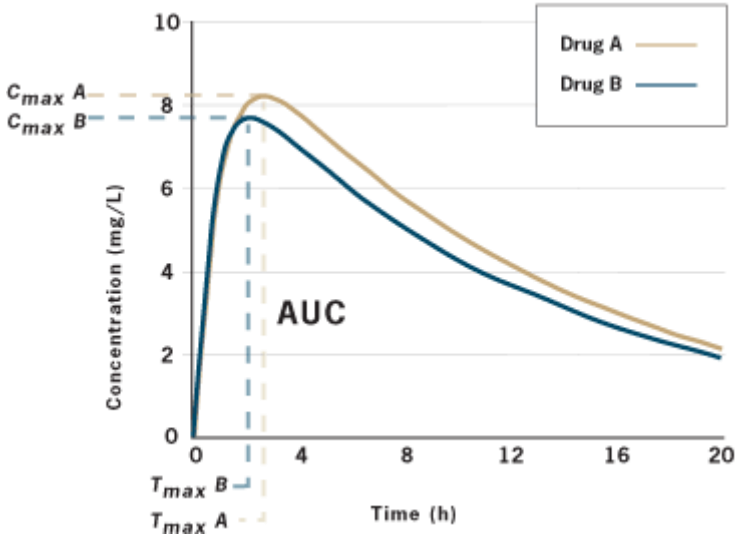

Figure 9: Model graph of comparison between innovator and generic products.

Bioequivalence is based on a comparison of ratios where the ratio of generic to innovator for each pharmacokinetic variable does not differ by more than 8:10, this is how the range for the confidence intervals is defined:

8/10 = 0.80 gives the lower limit

10/8 = 1.25 gives the upper limit

The 90% confidence intervals for the ratios of both Cmax and AUC should be contained within the limits 0.80–1.25 . Thus bioequivalence is based on ratios where the nominal equality is 1. It is not based on differences in absolute values. In practice, the generic product should have a ratio of mean values (AUC and Cmax generic: innovator) close to 1, indicating equality. If the observed ratio is closer to 0.8 or 1.25, then the data would have to contain little or no variation from the mean for the 90% confidence intervals of the ratio to lie in the 0.8 to 1.25 range that is necessary to demonstrate bioequivalence.

Conclusion:

Here we have studied the similarities and differences in drug approval process & requirements of the documents/CTD specifications to the drug regulatory authorities in the Europe, USA and India also submission and work flow related to bioavailability and bioequivalence studies was studied. CTD would provide a common format for the technical documentation that would significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and would ease the preparation of electronic submissions further simplifies exchange of regulatory information between regulatory authorities.

Conflict of Interest:

Authors have no conflict of interest from any point of view.

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