Review Article

Study of Drug Regulatory Approval Process and Comparative Requirement of Common Technical Documents (CTD) in Europe, USA and India in Coordination with Drug Developmental Process

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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. Various government agencies are involved in regulating drugs within their market, namely, USFDA-US, EDQM-Europe, TGA-Australia, MHRA-UK and TPD-Canada. A regulatory affair is becoming increasingly influential in the overall drug development process and is increasingly populated by highly trained scientists and medical professionals. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of drugs. This article will focus the similarities and differences in drug approval process of Europe, USA & Indian regulatory bodies. Years ago, a regulatory affair was often just a place where paperwork was done. There is still a lot of paperwork, although much of it is now in electronic format, but science and strategy now take precedence. So this paper point up the comparative regulatory approval process & requirements of the documents/CTD specifications to the drug regulatory authorities in the Europe, USA and India.

Keywords: Regulatory Approval, CTD, FDA, EU, CDSCO.

INTRODUCTION

Drug Development is long, risky, expensive, and these characteristics mean regulatory affairs has forceful emphasis to improve safety, efficacy, quality of the medicinal product. A new drug molecule can cost several millions of rupees or dollars to progress and any blunder causes greater impact on company's status. As medicines play a vital role in human's life there must be regulations for medicines ensuring Quality, Safety and Efficacy of drugs.[1] The regulatory affairs authorities are the only one who is completely responsible for holding products in compliance and maintaining all the records. So for the same purpose regulatory bodies given emphasis on the origin of the product and its requirement, preclinical studies, formulation and development, clinical studies as phase I to phase IV[2].

One of the vital activities of the regulatory authority is to ensure that the all the information regarding medicines has been correctly established to the patient covering labeling also. Even a small mistake in any of the activities related to regulatory can make the product to be recall in addition to loss of several millions of the money.[4]

Drug development to 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. Regulation affects all aspects of the pharmaceutical world, from independent innovators and pharmaceutical companies to regulatory and administrative bodies and patients also. Regulatory department in pharmaceutical industry is crucial link between company, products and regulatory authorities whose positive or negative standpoint foster the insight of the regulatory authority into the industry, for good or for bad. So, the better the scientific precision, the greater will be the chances for a product to come to the market within the expected time.

Regulatory importance is growing very rapidly in the pharmaceutical sector; need of PRA professionals to cater to the current needs of industries globally is increasing. Pharmaceutical industry is in immense need of professionals capable of handling issues related to regulatory affairs in a comprehensive manner. MNCs abroad are looking to India as their preferred destination for drug development, research activities and contract research organizations. A regulatory affair is a dynamic, rewarding field that embraces both scientific and legal aspects of drug development; plays a lead and pivotal role in drug development and research activities. There is a need to incorporate the current requirements of pharmaceutical updates incorporated by the regulatory bodies. [4]

Regulation involves extensive evaluation of a particular drug product to ensure protection of public health, promotion of the product, Drug registration, marketing authorization, import and distribution, pharmacovigilance.

Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health, by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.

Table 1: The following table shows the regulatory bodies as per the country.

Country	Regulatory Authority	
India	CDSCO	Central Drugs Standard Control Organization
Europe	EDQM	European Directorate for Quality of Medicines.
	EMEA	European Medicines Evaluation agencies.
UK	MHRA	Medicines and Health care products regulatory Agency.
Australia	TGA	Therapeutic Goods Administration.
Japan	MHLW	Japanese Ministry of health, Labour and Welfare.
Canada	HC	Health Canada
Brazil	ANVISA	Agency Nacional degradation Vigilancia Sanitaria.
South Africa	MCC	Medicines Control Council.
USA	FDA	Food and Drug Administration.

Regulatory Affairs takes 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.[4] So, this paper reviews here for the updated comparative drug approval process and common technical document (CTD).

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.[4-7] 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 new drug may have cost many millions of pounds, Euros or dollars to develop and even a three-month delay in bringing it to the market has considerable financial considerations. Even worse, failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall.[8]

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.[4]

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.

REGULATORY APPROVAL & SUBMISSION PROCEDURE IN USA

The FDA Drug and Biologic Approval Process:[9]

In 1820, the new era of USA drug regulation was started with the establishment of U.S. Pharmacopoeia. In 1906, Congress passed the original Food and Drugs Act, which require that drugs must meet official standards of strength and purity. However, in 1937, due to sulphanilamide tragedy, the Federal Food, Drug and Cosmetic Act (of 1938) was enacted and added new provisions that new drugs must be shown safe before marketing. Further, in 1962, the Kefauver-Harris Amendment Act was passed which require that manufacturers must prove that drug is safe and effective (for the claims made in labeling).

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 1 represents the new drug approval process of FDA.

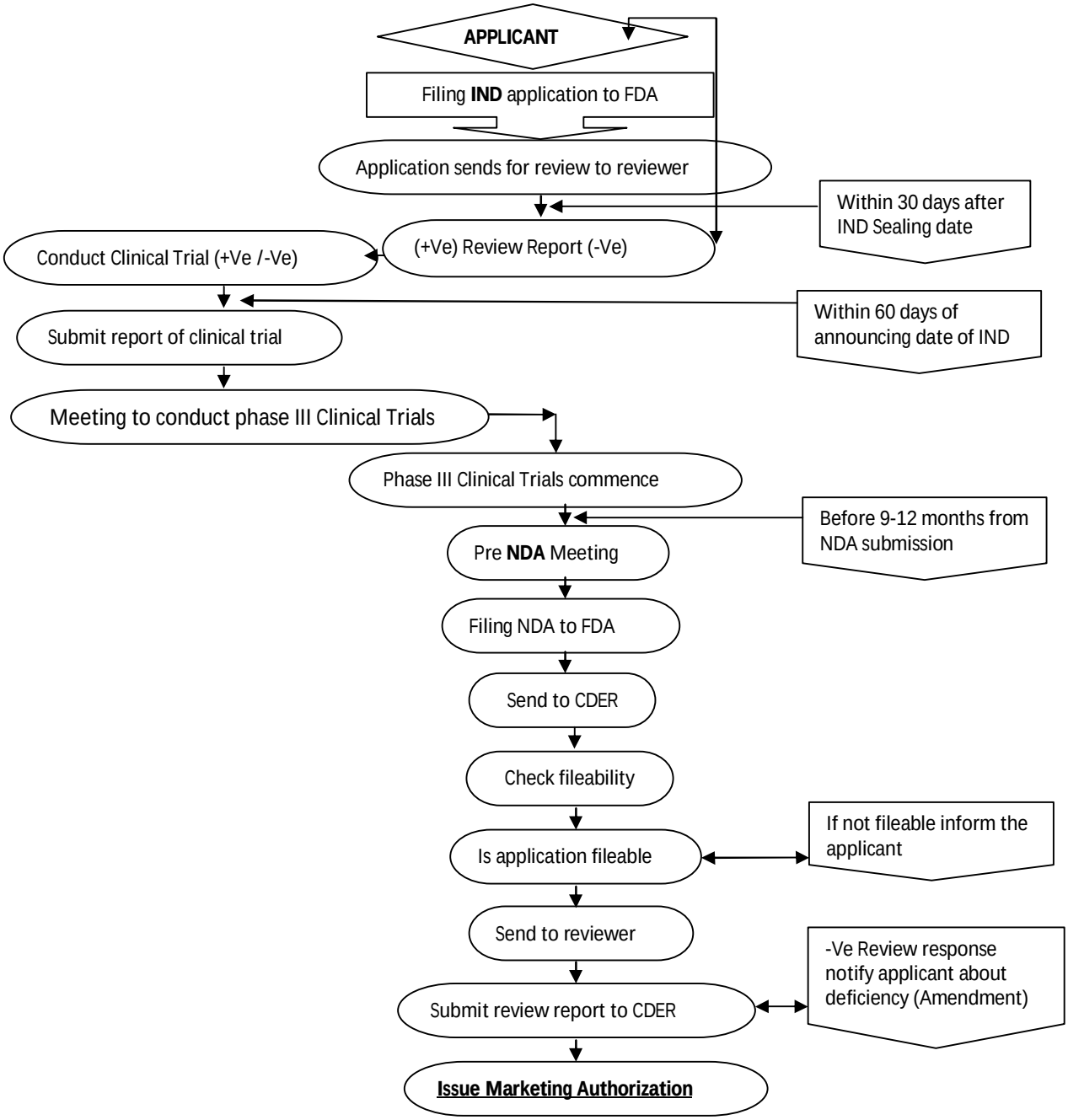

Figure 1: Flow Chart for Drug approval Process in USA

In order for pharmaceutical and biotech companies to market their drugs and biologics, companies must receive **FDA approval**, a rigorous, expensive, and time consuming process that can take over a decade to complete. **Of 5000 compounds discovered in the pre-clinical stage, only about 5 will make it through the entire FDA approval process. Therefore,** companies have to cover not only the cost of successful development of a single drug, but of many drugs that never make it to market.

The Phases in the FDA Approval Process[10]

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: [11]

- Correct dosage level
- 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)

If the drug proves to be safe and effective, the company then files an **NDA** or **BLA** with the FDA. 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.

REGULATORY APPROVAL & SUBMISSION PROCEDURE IN EUROPE (EU)

Pharmaceutical companies of EU use three approval procedures to market their pharmaceuticals. [11]

A) Centralized

B) Decentralized

C) Mutual recognition procedure

(A) Centralized Procedure

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. [12] 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 began to make the medicine available to the patients and healthcare professional in the EU countries. The following flow diagram illustrates the time & procedure to get approvals in Europe.[10,13]

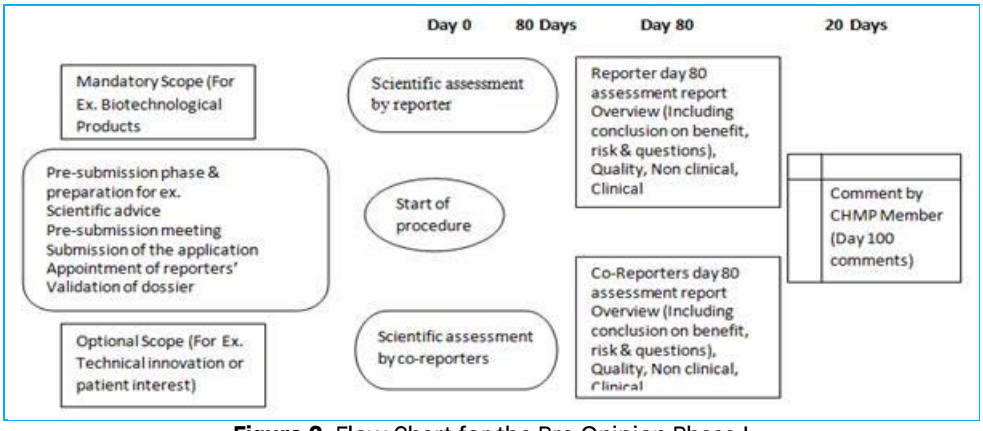

Figure 2: Flow Chart for the Pre Opinion Phase I

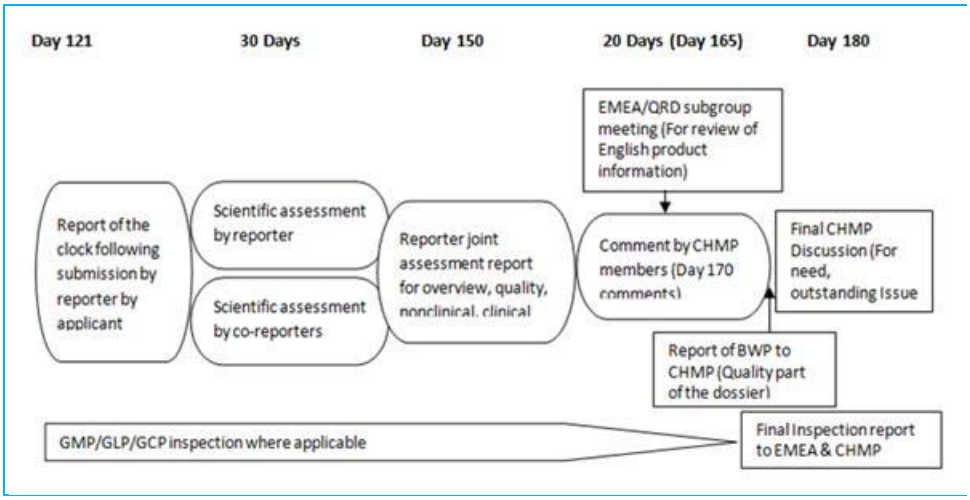

Figure 3: Flow Chart for the Pre Opinion Phase II

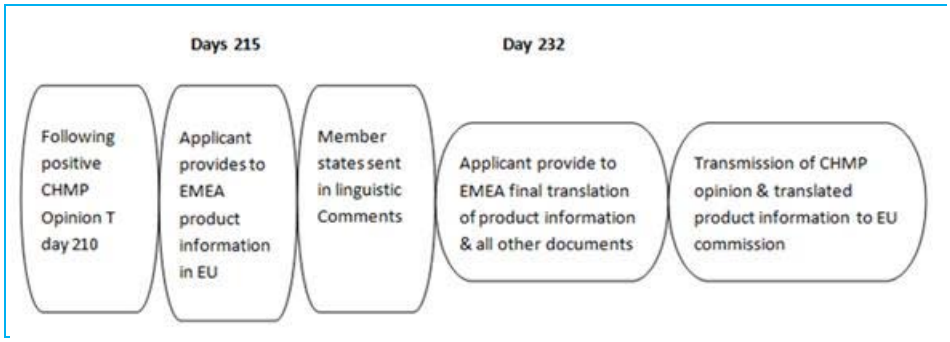

Figure 4: Flow Chart for the Post Opinion Phase

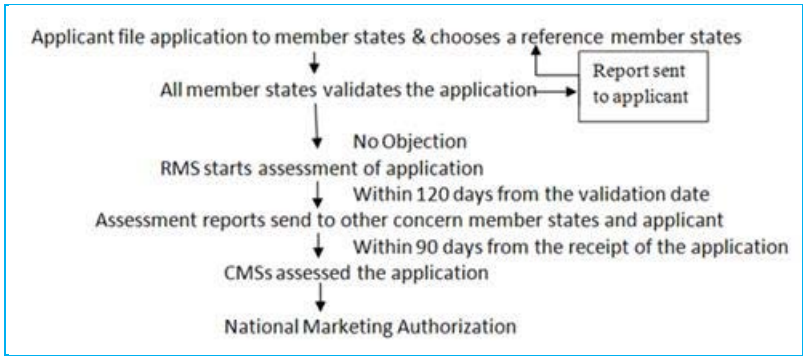

Figure 5: Required time & conversation between regulatory bodies, applicant in Decentralized Procedure

(B) Decentralized Procedure

An applicant can go directly to a national marketing authority to obtain permission to market its product in that member state and then seek to have other member states accept the marketing approval of the first member state.

(C) Mutual Recognition Procedure (MRP)

Used in order to obtain marketing authorizations in several Member States where the medicinal product in question has received a marketing authorization in at least one Member State at the time of application. The mutual recognition procedure (MRP) is similar to the de-centralized procedure with some differences. The mutual recognition procedure is applicable to medicinal products which have received a marketing authorization in any member state whereas the decentralized procedure is applicable to those products which were never approved in any member states of the European Union. The MRP is used to obtain marketing authorizations in various several member states. The evaluation of application by RMS can be taken within 90 days instead of 120 days (in decentralized procedure)[33]. After the grant of marketing authorization, the product can be marketed, which may be called as Phase IV trials, wherein new uses or new populations, long-term effects etc. can be explored.

REGULATORY APPROVAL & SUBMISSION PROCEDURE IN INDIA

The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control

Organization (CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] was established. In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945. Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure. The changes includes, establishing definitions for Phase I–IV trials and clear responsibilities for investigators and sponsors[31]. 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[32].

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[32]. The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3-4 centers) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centers, If the new drug substance is not marketed in any other country[32]. The new drug registration (using form number 44 along with full pre-clinical 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 10 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[33].

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 CTA application, 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 as 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.

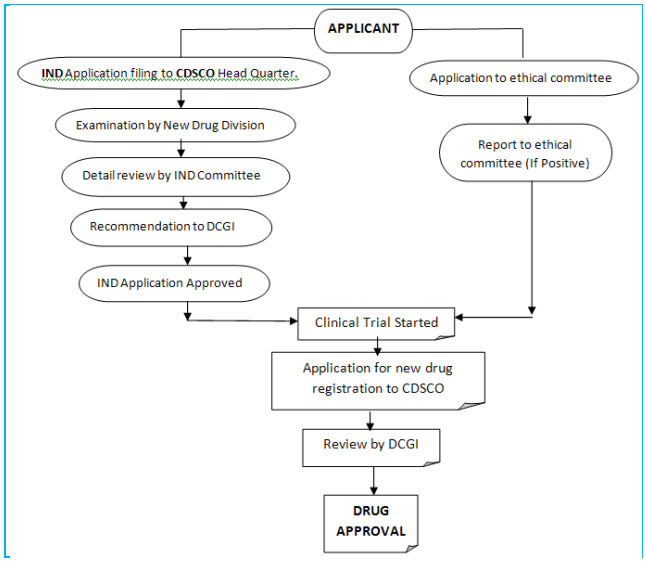

Figure 6: Flow Chart for the Drug Approval process in India

COMMON TECHNICAL DOCUMENTS (DOSSIER)

Dossier is a file document submitted for the approval of new drug or drug product. It is submitted in form of CTD. CTD is a harmonized format (template) for presenting data in the ICH regions. In some country it is optional. The process of reviewing & assessing dossier to support a medicinal product in view of its marketing (also called licensing, registration, approval, etc.), obviously 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. [15,16]

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. Although they may not be associated with a particular company, generic drugs are subject to the regulations of the governments of countries where they are dispensed. Generic drugs are labeled with the name of the manufacturer and the adopted name (nonproprietary name) of the drug.

A generic drug must contain the same active ingredients as the original formulation. 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.[3] 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. When generic products become available, the market competition often leads to substantially lower prices for both the original brand name product and the generic forms. The time it takes a generic drug to appear on the market varies. In the US, drug patents give 20 years of protection, but they are applied for before clinical trials begin, so the "effective" life of a drug patent tends to be between seven and 12 years. Prescriptions may be issued for drugs specifying only the chemical name, rather than a manufacturer's name; such a prescription can be filled with a drug of any brand meeting the specification. For example, a prescription for lansoprazole can be filled with generic lansoprazole, Prevacid, Helicid, Zoton, Inhibitol, or Monolitum. A generic drug of biological type (e.g. monoclonal antibodies), is different to chemical drugs because of its biological nature and it is regulated under extended set of rules for it; see Biosimilars.

Generic drug product is comparable to an innovator drug product- In dosage form Strength Route of administration Quality Use etc. 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. [17-20]

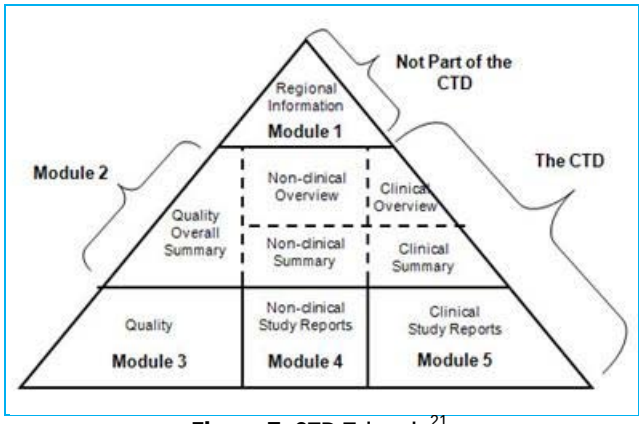

Figure 7: CTD Triangle[21]

The CTD is organized into five modules:

Module 1 is region specific. (Modules 2, 3, 4, and 5 are intended to be common for all regions.)

Module 1.

Administrative Information should contain documents specific to each region; e.g. application forms or the proposed label for use in the region.

1.1 Table of Contents

1.2 Documents Specific to Each Region (for example, application forms, prescribing information,)

Module 2.

CTD Summaries Begin with a general introduction to the pharmaceutical (its pharmacological class, mode of action, proposed clinical use. It contains 7 sections in the following order:

2.1 Common Technical Document Table of Contents (Modules 2-5)

2.2 CTD Introduction

2.3 Quality Overall Summary

2.4 Non-clinical Overview

2.5 Clinical Overview

2.6 Non-clinical Written and Tabulated Summaries

2.7 Clinical Summary

Module 3. Quality

3.1 Table of Contents of Module 3

3.2 Body of Data [Drug Substance, Drug Product & Regional information]

3.3 Literature References

Module 4. Non clinical / preclinical study reports

4.1 Table of Contents of Module 4

4.2 Study Reports

4.3 Literature References

Module 5. Clinical Study Reports

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports (BA/BE)

5.4 Literature References

Table 2: Differences between European Country and USA Submissions

European Country	USA
There are the different agencies for the submission of application as European Medicines Evaluation Agency (EMEA), Administrative organization Committee for Medicinal Products for Human Use (CHMP) of the EMEA – scientific input National Health Agencies.	FDA only one.
There is provision of multiple registration procedure as centralized, decentralized, national and MRP.	Only one registration procedure.
TSE /BSE study data is required	Not required
Braille code is required on labeling	Not required

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.

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.

Submission Related to Stability

Following tables illustrates the stability zone as per the ICH guidelines and different guidelines to maintain the stability requirement in different country. As per the survey by several countries/ regions have revised their own stability testing guidelines for larger safety margin

(e.g. 30°C/75%RH as long-term storage condition) so for this reason ICH Q1F –For Zones III and IV (Hot & Dry or Hot & Humid) have withdrawn in June 2006.

Impact of this change on ICH Q1A (R2) is that intermediate testing condition is unchanged: 30°C/65% RH. On the decision of use of applicant 30°C/75% RH is acceptable.

SUBMISSION & WORK FLOW RELATED to BIOAVAILABILITY and BIOEQUIVALENCE STUDY

Bioavailability

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 (Figure 9).[23-25]

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.

Table 3: Comparative Submission Related Control of Finished Product

Parameters	Europe	USA	India
Justification	As per ICH Q6A		
Assay	95.0 to 105.0 %	90.0 to 100.0 %	90.0 to 110.0 %
Disintegration	Required	Not required	Required
Color identification	Required	Not required	Required
Water Content	Not required	Required	Required

Table 4: Comparative Submission Related Manufacturing and its Control

Controlling Parameters	Europe	USA	India
Batch Size	2 pilot scale plus 1 lab bath or minimum of 1 lakh units whichever is higher.	1 pilot scale or minimum of 1 lakh units whichever is higher.	3 pilot scale
Number of batches	Three	One	Three
Process Validation	Required	Not required at the time of submission	Required
Packaging	Not Required	Minimum of 1 lakh units	Not addressed

Table 5: ICH Stability Zones

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IV	Hot humid/tropical zone
Zone IVb	ASEAN testing conditions hot/higher humidity

Table 6: Long Term Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Zone I	21ºC ± 2ºC	45% RH ± 5% RH	12 Months
Zone II	25ºC ± 2ºC	60% RH ± 5% RH	12 Months
Zone III	30ºC ± 2ºC	35% RH ± 5% RH	12 Months
Zone IV	30ºC ± 2ºC	65% RH ± 5% RH	12 Months
Zone IVb	30ºC ± 2ºC	75% RH ± 5% RH	12 Months
Refrigerated	5ºC ± 3ºC	No Humidity	12 Months

Frozen	-15ºC ± 5ºC	No Humidity	12 Months

Table 7: Accelerated and Intermediate Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40ºC ± 2ºC	75% RH ± 5% RH	6 Months
Accelerated Refrigerated	25ºC ± 2ºC	60% RH ± 5% RH	6 Months
Accelerated Frozen	5ºC ± 3ºC	No Humidity	6 Months
Intermediate	30ºC ± 2ºC	65% RH ± 5% RH	6 Months

Table 8: Comparative data

Parameters	Europe	USA	India
Clause	Vulume 4, EU Guideline for medicinal product	21 CFR Part 210 and 211 /Q1A(R2)	ICH Q1F
Condition (LT – long term stability, AS – Accelerated stability, IS – Intermediate Stability testing)	25/60(LT-1st yr every three months. 2nd yr every sixth month. 3rd yr annually.), 40/75(AS-0,3,6 moths.), 30/65 (IS-0,6,9,12 months.)	25/60(LT-1st yr every three months. 2nd yr every sixth month. 3rd yr annually.), 40/75(AS-0,3,6 moths.), 30/65(IS-0,6,9,12 months.)	30/35 and 30/75
Duration for submission	6 months accelerated & 6 months long terms	3 months accelerated & 3 months long terms	6 months accelerated & 3 months long terms
Number of batches required	Two/three batches	Three batches	Three batches
Container Orientation	Packing which simulate the final packaging for storage & distribution.	Inverted and upright. Packing which simulate the final packaging for storage & distribution.	Packing which simulate the final packaging for storage & distribution.
QP Certification	Required	Nor required	Required
Zone requirement (ICH)	Zone I and II	Zone I and II	Zone IVa and IVb

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).[27,28]

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 internationally agreed standards for measuring and assessing bioequivalence. Acceptance Criteria for Bioequivalence[27,18,23,25]

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 (Figure 9).

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 (see Figure 2). 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.[30]

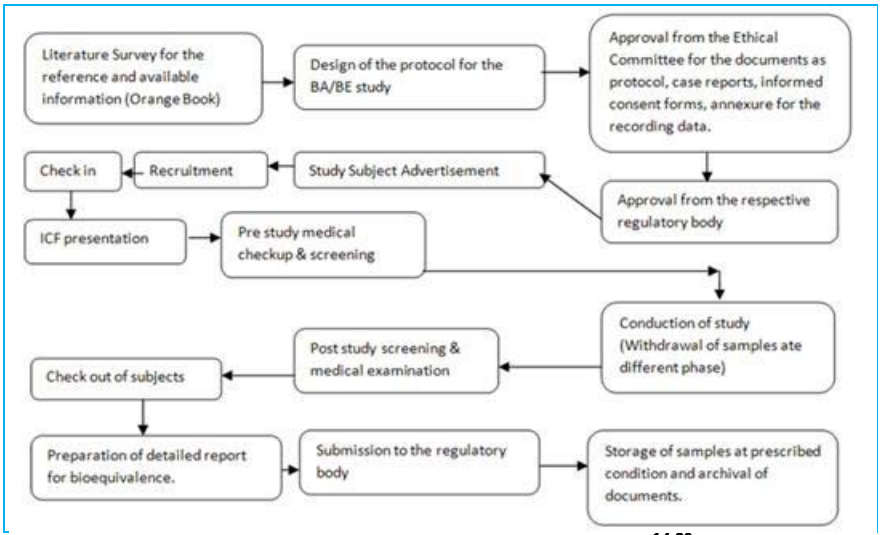

Figure 8: General Flow of Study at the CRO[14,20]

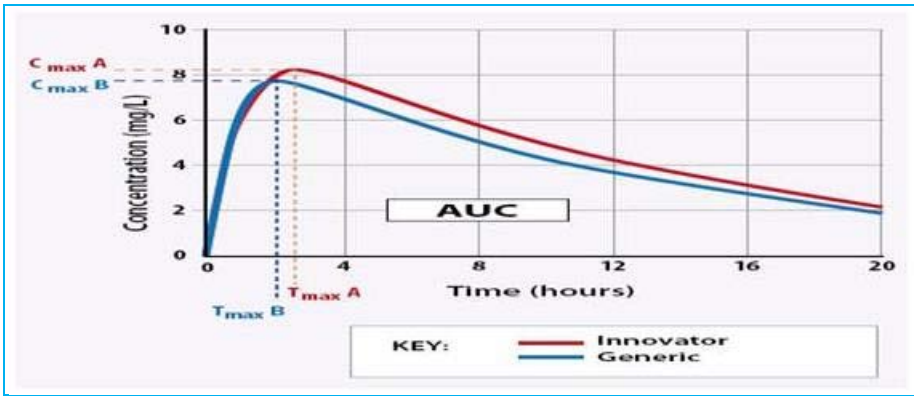

Figure 9: Model graph of comparison between innovator and generic products.

Table 9: Comparative data

Parameters	Europe	USA	India
Clinical research Organization (Audits)	Audited by MHRA	Audited by USFDA	Audited by CDSCO
Reserve Samples	Not required	5 times the samples required for analysis	-
Fasted / Fed Studies	Fed, fast & steady state required	Must be as per OGD recommendations	As CDSCO recommendation
Retention of Samples	No such requirement but usually followed	5 years from the date of filing the application.	3 years from the date of filing the application.
BE study for generic drugs	Against EU reference product (ERP) in any country	Against US RLD in any country. To refer 'BE recommendations' in FDA site for guidance.	Against US/EU/Australia RLD in any country except Thailand, where BE to be done locally against local reference product.

SUMMARY

In this paper we did individually study about the rule & regulations which are followed for drug approval process in USA, Europe & India. Also we did individually study for the specific requirement of data in CTD/Paper documents for the marketing authorization of pharmaceutical products. Data in the dossier gives the answer of following questions: What is the product? Is the quality presented acceptable on grounds of safety and efficacy? Is the quality presented reproducible? How long can the

quality be maintained? Quality must ensure consistency of safety and efficacy during the shelf life of all batches produced.

This paper summarizes here for the process of drug discovery procedure in brief & in co-ordination with the different regulatory authorities with Europe, USA, India.

And in last we did the comparative study. This comparative study of dossier compilation given a brief idea about the difference in regulatory requirements for drug approval process among USA, EU & India.

CONCLUSION

Here we conclude that the CTD and eCTD significantly reduces the time and resources needed to compile applications for registration of human pharmaceuticals. Eases the preparation of electronic submissions. Facilitates regulatory reviews and communication with the applicant by a standard document of common elements. Simplifies exchange of regulatory information between Regulatory Authorities etc.

Provide for a scientifically sound means of establishing the quality, safety and efficacy of therapeutic products. Improve the transparency, predictability and efficiency of the regulatory process. Contribute to reducing unnecessary regulatory burden and promoting industry compliance. Promote bilateral and multilateral regulatory communication and cooperation – common regulatory platform. Level playing field good for export market.

REFERENCES

1. CTD Guidelines map (ICH, EMEA AND FDA), website www.reg-info.com/ctd-guidelines. (assessed on 15th Jan 2013)
2. Drug price compitition & patent term restoration act of 1984, website http://www.cptech.org/ip/health/generic/ hw.html. (assessed on 1st march 2013)
3. 180-day generic exclusivity, website- ww.fda.gov/downloads/Drugs/Guidances/ucm079342.pdf
4. www.reg-info.com/(assessed on 4th march 2013)
5. www.raps.org (assessed on 1st March 2013)
6. www.topra.org (assessed on 1st March 2013)
7. www.capra.ca (assessed on 1st March 2013)
8. Quality in the Manufacture of Medicine and other healthcare products, Pharmaceutical press, chapter. 3, 29-41.
9. Revision History Module 1 Administrative informationwebsite- www.fda.gov/downloads/Drugs/ .../UCM163175.pdf
10. Submitting Marketing Applications According to the ICH-CTD Format - General Considerations, website- www.fda.gov/RegulatoryInformation/Guidances/ucm129703.htm
11. Matin s. lipsky, lisa k. sharp, The drug approval process, Jabfp, 14(5), sep-oct 2001.
12. Jaime R hornecker, Generic drugs: history, approval process and current challenges, 34(6), US pharm2009, 26-30.
13. Introduction - European Agency for the Evaluation of Medicinal products, website- www.emea.europa.eu/docs/ en_GB/...library/.../WC500074880.pdf REFERENCE.
14. Jaime R hornecker, Generic drugs: history, approval process and current challenges, 34(6), US pharm2009, 26-30.
15. Guidance for Industry - FDA, www.fda.gov/./Drugs/./Forms SubmissionRequirements/ElectronicSubmissions/UM163188.pdf
16. ICH Guideline: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality - M4Q; Quality Overall Summary of Module 2, Module 3: Quality, http://www.ich.org.
17. Generic drugs, website- www.wikipedia.org/wiki/generic-drug.
18. Welage LS kinking dm, ascione FJ, gaither CA. Understanding scientific issues embedded in the generic drug approval process, feb- may04(5), 2001. 114-30.
19. Lionberger RA., FDA critical path- initiatives, Opportunities for generic drug development. AAPSJ. 10(1), 2008, 103-9.
20. Welage L.S., in 2001, Understanding scientific issues embedded in the generic drug approval process Regulations regarding bioequivalence have been in place for more than 20 years, controversies over bioequivalence continue to arise.
21. CTD Guidelines map (ICH,EMEA AND FDA), website www.reg-info.com/ctd-guidelines.
22. www.cdsco.nic.in (assessed on 1st Jan 2013).
23. Peters JR,hixon DR, conner DP, davit BM, catterson DM, parise CM generic drugs-safe, effective and affordable dermotol ther. 22(3), 2009 may-jun, 229-40.
24. Filiz hinchal, An introduction to safety issues in biosimilars/follow-on biopharmaceuticals, Jmed cbr, 7(1), 2009.
25. Howland RH, Evaluating the bioavailability and bioequivalence of generic medications, J. psychosocial nursing and mental health serv. 48(1), 2010.
26. Filiz hinchal,in 2009, An introduction to safety issues in biosimilars / follow-on biopharmaceuticals Biopharmaceuticals are emerging global healthcare tools, which promise to provide effective treatment of many serious and life- threatening illnesses with their high specificity and activity; they are considered the future of drug therapy.
27. Bioequivalence and Generic Medicines Introduction, website- www.egagenerics.com/doc/zanen-biogenerics.pdf
28. Howland RH, 2010, Evaluating the bioavailability and bioequivalence of generic medications.
29. Jaime R hornecker, in 2009, Generic drugs: history, approval process and current challenges According to the FDA, a generic drug is a product that compares to the pioneer, or reference, drug product (usually a branded drug) in dosage form, route of administration, strength, quality, safety, and performance characteristics.
30. Chow sc lio.jp, Statistical assessment of biosimilar products. J.bio pharm stat, 20(1), 2010 Jan, 10-30.
31. http://www.clinpage.com/article/indias_regulation_timeline/C9. (Assessed on March, 3rd 2013).
32. http://infochangeindia.org/200909177947/Health/Analysis/Trial-by-fire.html. (Assessed on March, 3rd 2013).
33. European Commission: Notice to Applicants: Volume 2A; Procedures for Marketing Authorization; Chapter 2; Mutual Recognition http://www.imb.ie/images/uploaded/documents/ Chap2NTA.pdf. (Assessed on March, 3rd 2013).

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