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DOSSIER PREPARATION REQUIREMENTS FOR GENERIC DRUGS OF USA, EUROPE & INDIA

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Abstract:

Common Technical Document (CTD) provides a standardized structure for regulatory submissions that is acceptable in all ICH countries. Although the CTD makes multinational filings easier, there are significant differences in the dossier submission requirements in these countries. This study put forth the differences in registration requirements for generics in United States, Europe and India. Generic drugs in US they are approved under the Abbreviated New Drug Application. Bioavailability and Bioequivalence study data is critical in the generic drug approval process. For marketing authorization of the generic medicinal product in Europe, the applicant should submit abridged application to the relevant authority. The ability to accommodate country specific requirements and understand regulatory differences will have a substantial impact on the success of its multi country submissions strategy. Generic manufacturers must file an Abbreviated New Drug Submission (ANDS), and the CDSCO is controlled and governed by Directorate General of Health Services which comes under ministry of health and family welfare, Government of India. Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approval procedures.

Keywords: *CTD, Generic drug, CDSCO, Bioequivalence, ANDS.*

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1. INTRODUCTION:

1.1. COMMON TECHNICAL DOCUMENT (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 countries, 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 is 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 [1,2].

Dossier is a file document submitted based on the requirement of regulatory agency for the approval of drug product. It is essential to submit dossier file in the form of common technical document in USA and EUROPE. Generic drugs are approved under ANDA submission. An Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval for an existing licensed medication or approved drug. The ANDA contains data which when submitted to FDA's Centre for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. The European Medicines Agency (EMA) is a European agency for the evaluation of medicinal products. The EMA operates as a decentralized scientific agency of the European Union and is responsible for the protection and promotion of human and animal health, specifically through the coordination of evaluation and monitoring of centrally authorized products and national referrals, developing technical guidance and providing scientific advice.

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 analyses 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).

1.2. INTRODUCTION TO USFDA [3]:

The FDA is the government agency responsible for reviewing, approving and regulating medical products, including pharmaceutical drugs and medical devices. It also regulates various other products, including food, cosmetics, veterinary drugs, radiation-emitting products, biological products and tobacco.

Protecting public health is a key priority of the FDA, and for good reason. Tens of millions of Americans rely on prescription and over-the-counter drugs to stay healthy, with as many as 3 billion prescriptions written each year. Safety concerns prompt the FDA to pull one to two drugs and six to eight medical devices from the market annually.

All medications and medical devices come with inherent risks, but it is the FDA's duty to address serious risks that can be avoided and managed. Before any drug or medical device can gain approval to be sold in the United States, it must first meet the FDA's regulatory standards. The FDA reviews the safety and effectiveness of medical products not only before they are approved, but also after they are sold to consumers and used.

But FDA approval does not necessarily mean that a product is safe, or that its effectiveness has been confirmed in a clinical trial. The FDA clears some medical products if the manufacturer can prove they

are substantially like a product already on the market. Even with a system in place to ensure a new product's safety and minimize its risks, unexpected complications can arise. If adverse event reports or post-marketing surveillance indicate that a medical product is causing preventable injuries to consumers, the FDA can coordinate with the product's manufacturer to issue a recall.

1.3.EUROPEAN MEDICINES AGENCY [4]:

Founded in 1995, the European Medicines Agency (EMA) has worked across the European Union (EU) and globally to protect public and animal health by assessing medicines to rigorous scientific standards and by providing partners and stakeholders with independent, science-based information on medicines.

EMA has a 20-year track record of ensuring efficacy and safety of human and veterinary medicines across Europe, and promoting research and innovation in the development of medicines.

In its first two decades, the Agency recommended the authorisation of a total of 975 human and 188 veterinary medicines.

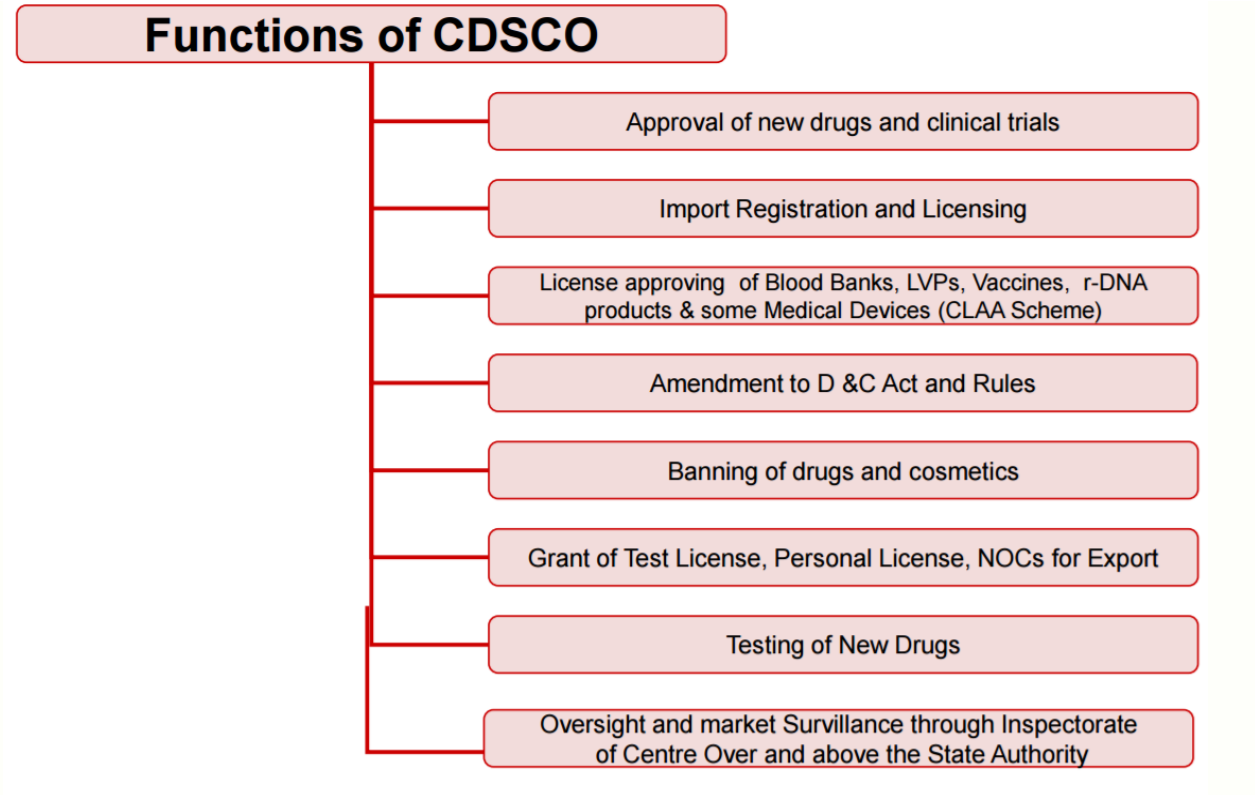
EMA's success is based on cooperation within the European medicines regulatory network – a unique partnership between the European Commission, the medicines regulatory authorities in the European Economic Area countries, and EMA. Working together has encouraged the exchange of knowledge, ideas and best practices, to ensure the highest standards in medicines regulation.

Today, seven EMA scientific committees and more than 30 working parties provide scientific expertise for the regulation of medicines by drawing on a pool of several thousand European scientific experts from the network.

1.4. CENTRAL DRUG STANDARD CONTROL ORGANIZATION [5]:

The Central Drugs Standard Control Organization (CDSCO) is the Central Drug Authority for discharging functions assigned to the Central Government under the drugs and cosmetic act.

CDSCO has 6 zonal offices, 4 sub zonal offices and13 port offices and several labs under control.



ROLES AND RESPONSIBILITIES:

CDSCO stands for Central Drugs Standard Control Organization. CDSCO is a licensing authority, a regulatory agency which approves any new chemical entity (drug) which is to be imported to India.

Authority: Who is Who?
CDSCO is controlled and governed by Directorate General of Health Services which comes under ministry of health and family welfare, Government of India. The headquarter of the Central Drugs Standard Control Organization is located at New Delhi, while it has multiple zonal offices throughout India. CDSCO also works in close context with Central Drug Laboratories to perform quality control tests.
To regulate imported drugs as authority, the CDSCO works with the Drugs Technical Advisory Board and the Drugs Consultative Committee, while the Central Drugs Laboratory undertakes testing of such drugs.
The central authorities are responsible for approval of new drugs, clinical trials in the country, laying down the standards for drugs, control over the quality of imported drugs, coordination of the activities of State Drug Control Organizations and providing expert advice with a view of bringing about the uniformity in the enforcement of the Drugs and Cosmetics Act. The state authorities on the other hand are concerned with the regulation of manufacture, sale and distribution of Drugs licensing drug testing laboratories, approving drug formulations for manufacture, carrying out pre- and post-licensing inspections, and overseeing the manufacturing process, for drugs manufactured by respective state units and those marketed in the state. These authorities are formed under the Drug and Cosmetics Act 1940 and Rules 1945.
Functions undertaken by the central authority can be summarized as:

1. Laying down standards of drugs, cosmetics, diagnostics and devices.
2. Laying down regulatory measures, amendments to Acts and Rules.
3. To regulate market authorization of new drugs.
4. To regulate clinical research in India.
5. To approve licenses to manufacture certain categories of drugs as Central Licence approving Authority i.e. for Blood Banks, Large Volume Par-enterals and Vaccines & Sera.
6. To regulate the standards of imported drugs.
7. Work relating to the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC).
8. Testing of drugs by Central Drugs Labs
9. Publication of Indian Pharmacopoeia.

Functions undertaken by the state authorities can be summarized as:

1. Licensing of drug manufacturing and sales establishments
2. Licensing of drug testing laboratories.
3. Approval of drug formulations for manufacture.
4. Monitoring of quality of Drugs & Cosmetics, manufactured by respective state units and those marketed in the state.
5. Investigation and prosecution in respect of contravention of legal provisions.
6. Administrative actions.
7. Pre- and post- licensing inspection
8. Recall of sub-standard drugs.

2.DOSSIER PREPARATION REQUIREMENTS FOR US GENERIC DRUGS[5,6]:

Source: http:/ /www.fda.gov/cder/org.htm

DEFINITION:
A drug product that is comparable to a brand/reference listed drug product in a dosage form, strength, route of administration, quality and performance characteristics and intended use.

WHEN GENERIC DRUGS CAN BE MARKETED:
1)after patent and exclusivity protection ends.

2)patent owner waives its rights, and

3)FDA requirements are met.

WHAT ARE THE BASIC GENERIC DRUG REQUIREMENTS?

Same active ingredients

Same route of administration

Same dosage forms

Same strength

Same condition of use

Inactive ingredients already approved in a similar NDA

ANDA REQUIREMENTS[7]:
1)labelling
2)pharm /TOX
3)chemistry
4)manufacturing
5)controls
6)microbiology
7)inspection
8)testing
9)bioequivalence

LABELLING:

- Same as brand name labelling
- May differ in excepients and product description

PHARM/TOX:

- All the active ingredients must be approved in either the reference listed drug or the similar NDA in same or higher levels.
- Generic focus- is there anything unique to using these ingredients in the proposed generic.

CHEMISTRY, MANUFACTURING, CONTROL:

- components and control
- manufacturing and control
- Batch formulations and records
- Descriptions of facilities
- Specifications and testing
- Packaging
- Stability

MICROBIOLOGY:

Assure that sterility of the product through the manufacturing process-especially in the injectable drug products.

INSPECTION AND TESTING:

Assure the adherence to and authenticity of the data submitted in the application.

Assure manufacturing facility are in compliance with cGMP.

Assure BE sites are in compliance with cGMP.

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Centre for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public[7].

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).*

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Waxman-Hatch Act. This Act expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials. At the same time, the brand-name companies can apply for up to five additional years longer patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process. Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.

The Office of Generic Drugs home page provides additional information to generic drug developers, focusing on how CDER determines the safety and bioequivalence of generic drug products prior to approval for marketing. Generic drug application reviewers focus on bioequivalence data, chemistry and microbiology data, requests for plant inspection, and drug labelling information.

Through an Abbreviated new drug application (ANDA) process, applicant may get FDA approval for a generic drug without conducting clinical trials if the drug is bioequivalent to the branded (innovator) drug. All generic drugs approved by FDA have the same high quality, strength, purity and stability as brand name drugs.

TYPES OF ANDA[8]:

ParaI
ParaII
ParaIII
Para IV:

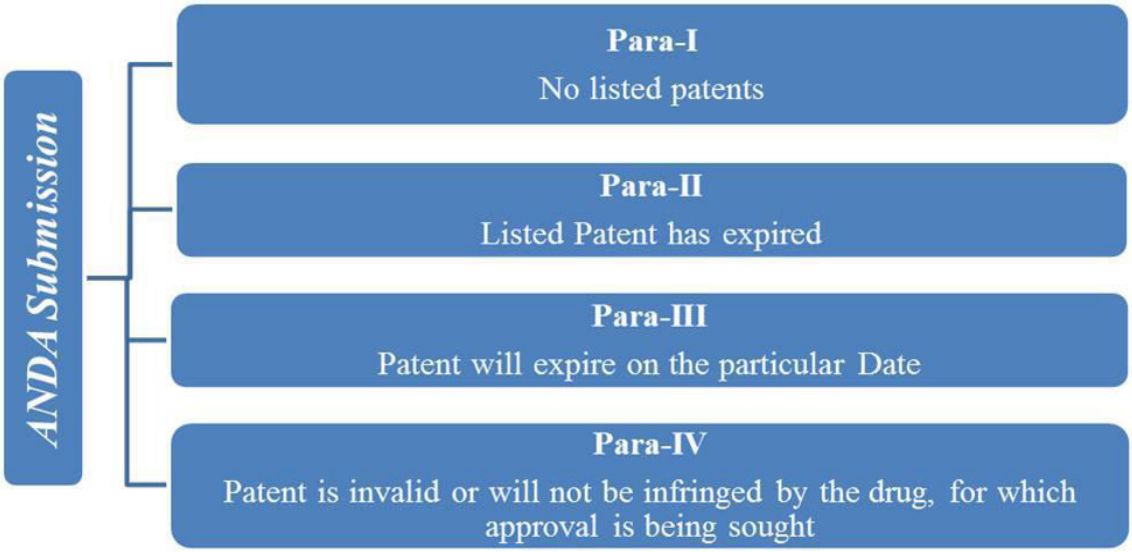


Fig-1-Types of ANDA

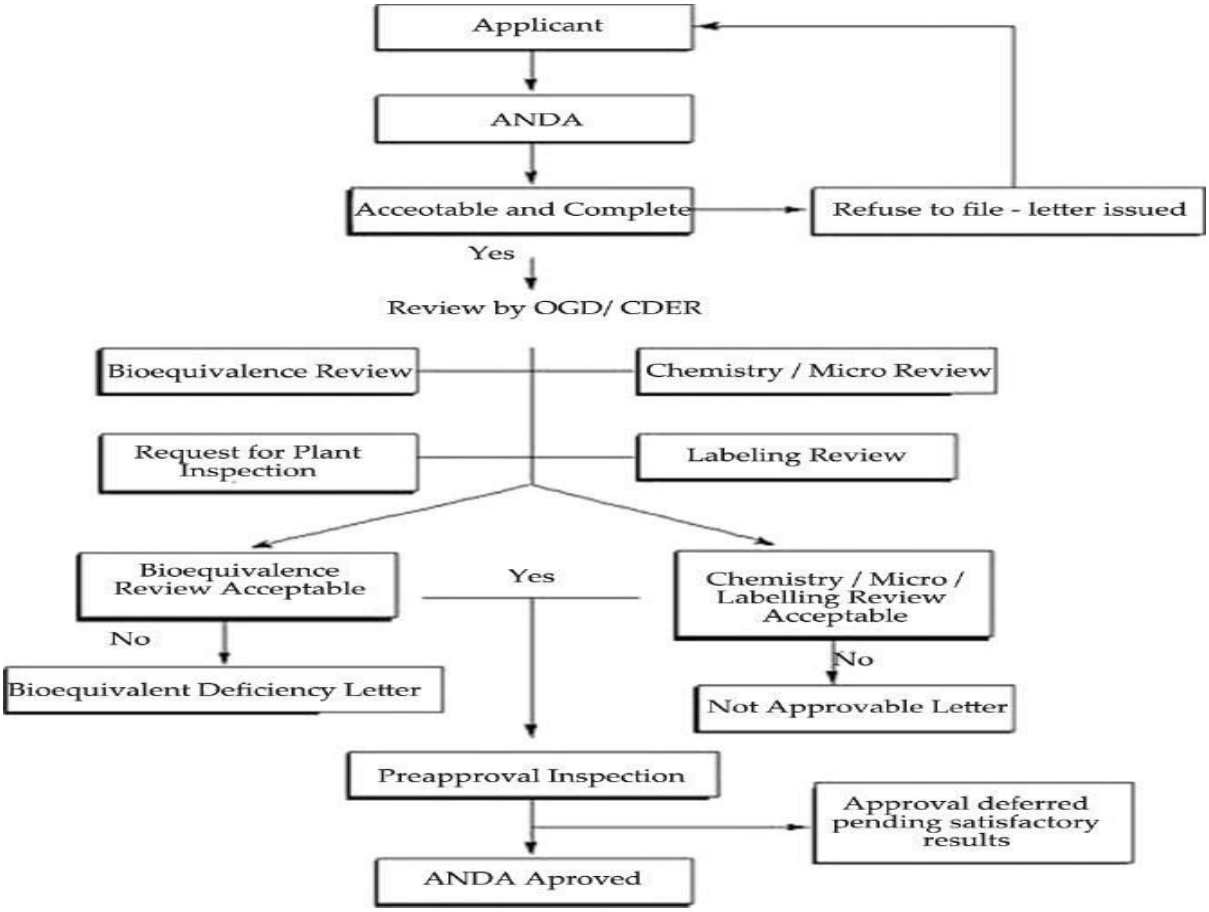


Fig-2- ANDA Application Process

2.1. EMA – MARKETING DRUG AUTHORIZATION APPLICATION (MAA)[9]

www.ema.europa.eu

The EU has one of the most highly regarded regulatory systems in the world. The system comprises of European parliament, the council of ministers, and the European Commission. EU consists of 27 member states: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Iceland, Norway, and Liechtenstein.[8] These EFTA members are those countries which were unable to join rest of the 27 member states as common market. These three EFTA member countries along with 27 EU member states, comprises of the European Economic Area (EEA). The European Medicines Agency is a decentralized agency of the European Union, located in London.[8] The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union and applications for European marketing authorizations for both human and veterinary medicines (centralized procedure). Under the centralized procedure, companies submit a single marketing-authorization application to the Agency. Once granted by the European Commission, a centralized (or "Community") marketing authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). The European parliament approves the laws together with the council of ministers. The council of ministers is the voice of Member states and is responsible for enactment of directives.

MODULE 1 - ADMINISTRATIVE INFORMATION[9,10] :

CTD	EU CTD
1.0	Cover Letter
1.1	Comprehensive table of content
1.2	Application Form
1.3	Product Information
1.3.1	Summary of Product Characteristics, Labelling and Package Leaflet
1.3.2	Mock-up
1.3.3	Specimen
1.3.4	Consultation with Target Patient Groups
1.3.5	Product Information already approved in the Member States
1.3.6	Braille
1.4	Information about the Experts
1.4.1	Quality
1.4.2	Non-clinical
1.4.3	Clinical

European Generics Association (EGA)

The EGA is the official representative body of the European generic and pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

- EGA represents generic pharmaceuticals companies and their subsidiaries from throughout Europe, either directly or through national associations.
- The EGA and its members work with the European national governments and the EU institutions to develop affordable solutions for pharmaceutical care and to increase Europe 's competitive strength in the global pharmaceutical medicines market.
- For the Marketing Authorization of Generic medicinal product in Europe, the applicant should submit Abridged application to the authority.
- Marketing authorization for a pharmaceutical product in more than one country in the European Union must currently be applied for through one of two procedures: either the —Centralized Procedure or the —Mutual Recognition Procedure (MRP). A third, the —Decentralized Procedure, came into force with the newly revised EU pharmaceutical Directive in November 2005.

MARKETING AUTHORIZATION PROCEDURES:

Authorization of medicines is done by four procedures:

- Centralized Procedure
- Mutually Recognition Procedure
- Decentralized Procedure
- National Procedure

1.5	Specific Requirements for different types of applications
1.5.1	Information for bibliographical applications
1.5.2	Information for Generic, "Hybrid" or Bio-similar Applications
1.5.3	(Extended) Data/Market Exclusivity
1.5.4	Exceptional Circumstances
1.5.5	Conditional Marketing Authorisation
1.6	Environmental risk assessment
1.6.1	Non-GMO
1.6.2	GMO
1.7	Information relating to Orphan Market Exclusivity
1.7.1	Similarity
1.7.2	Market Exclusivity
1.8	Information relating to Pharmacovigilance
1.8.1	Pharmacovigilance System
1.8.2	Risk-management System
1.9	Information relating to Clinical Trials
	Responses to Questions
	Additional data

2.2. CDSCO (central drug standards control organization)[11]

A generic drug (generic drugs, short: generics) is a drug defined as "a drug product that is comparable to brand/reference listed drug 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. A generic drug must contain the same active ingredients as the original formulation. Per 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 pharmacodynamics properties. A generic drug is identical--or bioequivalent--to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. Opportunities arising from increased use of generics

Ensuring the sustainability of the generic medicines industry is one of the key elements in maintaining broad access to medicines for all. To meet increasing demand from more patients who are living longer and expecting an improved quality of life, generic medicines offer quality treatment at affordable prices.

To ensure sustainability both investment in the generics sector and incentives for generic prescribing/dispensing are required to increase the market share of generics.

3. THE COMMON TECHNICAL DOCUMENT (CTD)[12]:

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. It is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, U.S.) and the Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use.

The Common Technical Document is divided into five modules:

1. Administrative and prescribing information
2. Overview and summary of modules 3 to 5
3. Quality (pharmaceutical documentation)
4. Preclinical (Pharmacology/Toxicology)
5. Clinical - efficacy (Clinical Trials)

4.GENERAL CONSIDERATIONS FOR DOSSIER PREPARATION [9,10]

- The CTD is only a format for submission of information to CDSCO.
- Although adherence to overall CTD structure is necessary, it should be noted that no guideline can cover all eventualities, and common sense and a clear

focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format at some of the subsection levels, if needed to provide the best possible presentation of the information, to facilitate the understanding and evaluation.

- Text and tables should be prepared using margins that allow the document to be printed clearly without losing any information and the left-hand margin should be sufficiently large so that information is not obscured by the method of binding.
- Font sizes for text and tables should be of a style and size that are large enough to be easily readable. Times New Roman, 12- point font is recommended for descriptive text and Times New Roman, 9 to 10-point font for table contents and text.
- All abbreviations should be defined at the first instance they are used and listed at the end of the dossier.
- References should be cited in accordance with the current edition of the uniform requirements for manuscripts submitted to biomedical journals, International Committee of Medical Journal Editors (ICMJE).

5.DIFFERENCES BETWEEN USFDA, EMA AND CDSCO

Table 1: Principle differences between US, EU & INDIA

Requirements	US	EU	INDIA
Agency	One Agency USFDA	Multiple Agencies • EMEA • CHMP • National Health Agencies	One Agency DCGI
Registration Process	One Registration Process	Multiple Registration Process • Centralized (European Community) • Decentralized (At least 2 member states) • Mutual Recognition (At least 2 member states) • National (1 member state)	One Registration Process
TSE/BSE Study data	TSE/BSE Study data not required	TSE/BSE Study data required	TSE/BSE Study data required
Braille code	Braille code is not required on labelling	Braille code is required on labelling	Braille code is not required on labelling
Post-approval changes	Post-approval changes in the approved drug: • Minor changes • Moderate changes • Major changes	Post-variation in the approved drug: • Type IA Variation • Type IB Variation • Type II Variation	Post approval changes: Major quality changes Moderate quality changes

Table 2: Administrative Requirements

Requirements	US	EU	INDIA
Application	ANDA / NDA	MAA	MAA
Debarment classification	Required	Not Required	Not Required
Number of copies	3	1	1
Approval Timeline	~18 Months	~12 Months	12 - 18 Months
Fees	Under $2 million-NDA Application $51,520 – ANDA Application	National fee (including hybrid applications): £103,059 Decentralised procedure where UK is CMS: £99,507	50,000 INR
Presentation	eCTD & Paper	eCTD	Paper

Table 3: Finished Product Control Requirements

Requirements	US	EU	INDIA
Justification	ICH Q6A	ICH Q6A	ICH Q6A
Assay	90 - 100 %	95 - 105 %	90 - 110 %
Disintegration	Not Required	Required	Required
Colour Identification	Not Required	Required	Required
Water Content	Required	Not Required	Required

Table 4: Manufacturing & Control Requirements

Requirements	US	EU	INDIA
Number of batches	1	3	1
Packaging	A minimum of 1,00,000 Units	Not Required	Not addressed
Process Validation	Not required at the time of submission	Required	Required
Batch Size	1 pilot scale or minimum of 1 lakh units whichever is higher.	2 pilot scale plus 1 lab batch or minimum of 1 lakh units whichever is higher.	Pilot scale batch

Table 5: Stability Requirements

Requirements	US	EU	INDIA
Number of batches	3 Pilot Batch or 2 Pilot Batch & 1 Small scale	2 Pilot Scale (If API Stable) 3 Primary Batches (If API unstable)	2 Pilot Scale/Production scale(If API Stable) 3 Primary Batches (If API unstable)
Condition: Long term stability, Accelerated stability,	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months); Intermediate: 30°C/65%RH	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months) Intermediate: 30°C/65%RH	Long term: 30°C/70%RH Accelerated:40°C/75%RH (0,3,6 months)
Minimum time period at Submission	6 Months Accelerate & 6 Months long term	6 Months Accelerate & 6 Months long term	6 Months Accelerate & 6 Months long term
Container orientation	Inverted & Upright	Do not address	upright and inverted
Clause	21 CFR part 210 & 211	Volume 4 EU Guidelines for medicinal products	ICH Q1F
QP Certification	Not Required	Required	Required

Table 6: Bioequivalence Requirements

Requirements	US	EU	INDIA
CRO (Audits)	Audited by FDA	Audited by MHRA	CDSCO
Reserve Sample	5 times the sample required for analysis	No such requirement	-
Fasted / Fed	Must be as per OGD recommendation	No such requirement	As CDSCO recommendation
Retention of samples	5 years from date of filing the application	No such requirement	3 years from date of filing the application
BE study for generic drugs	Against US RLD in any country. To refer 'BE recommendations' in FDA site for guidance.	Against EU reference product (ERP) in any country	Against US/EU/Australia RLD in any country except Thailand, where BE to be done locally against local reference product.

6. RESULTS AND DISCUSSION:

INDIAN MARKET:

The CDSCO defined the procedure to obtain product approval (dossier) With the following information. For the existing molecule if a manufacturer wanted an approval then the firm should submit their application form along with manufacturing formula, brief manufacturing procedure, minimum 3 months accelerated stability studies data, testing procedure with specification, technical competent staffs details for manufacturing and testing, products label details, marketed products labelling information.

Prior to grant of the dossier approval or product approval to manufacture and supply for an existing molecule, the staffs drug control department schedule for the manufacturing facility inspection to verify for the Cgmp adherence of the revised schedule m.

The manufacturing facility must have own testing unit including microbiology section otherwise need to establish with a commercial testing lab.

Every commercial batch must be tested as per IP if its official in pharmacopoeia or as per in house specification prior to distribution.

USA MARKET:

As per USFDA guidelines, to obtain approval for ANDA the dossier shall contain the following information.

Product development details including formulation development, analytical development and stability studies details. A master batch record, process validation protocol, testing procedures along with specification, stability protocol etc need to be made ready prior to start of the batch.

The same batch shall be subjected for bioequivalence studyalong with RLD, stability studies. While executing this submission batch the manufacturing process shall be validated with stratified sampling process. All the above mentioned documents are to be attached with dossier along with intended batch record specifying the batch size, equipments to be used for commercial manufacturing if its different from the submission batch manufacturing. To file a ANDA and sanda the firm must tie up with an local office in USA to liaison with FDA. All communications from FDA are routed through local office.

EUROPE MARKET:

As per ema guidelines, to obtain approval for EMA the dossier shall contain the following information.

Product development details including formulation

development, analytical development and stability studies details. A master batch record, process validation protocol, testing procedures along with specification, stability protocol Etc need to be made ready prior to start of the batch. Minimum two batches need to be manufactured at the commercial batch size as exhibit/ submission batch. The same batch shall be subjected for bioequivalence study along with reference product collected from market, stability studies.

While executing this submission batches the manufacturing process shall be validated. The raw materials and primary packing materials used shall be free from TSE and BSE. All the above-mentioned documents are to be attached with dossier. To have 24 months as shelf life for the proposed product, the the proposed product, the firm must submit at least 12months real time stability study data. During commercial supply if the firm decides to scale up the batch size, then that shall be routed through variation. The product cant be approved until the patient expires. Also in Europe to obtain marketing authorization, the firm must submit at least 12 months real time stability study data. During commercial supply if the firm decides to scale Up the batch size, then that shall be routed through variation. The product cannot be approved until the brand patient expires. Also in Europe to obtain marketing authorization, the firm must have a registered office with in Europe which is operating full time basis.

7. REFERENCES:

1. www.regulatoryone.com2012/01/anda.html
2. www.fda.gov
3. www.ema.europa.eu/
4. www.prnewswire.com/news...../usagenericoutlook2018
5. S.M.Shakeel, Shaik Salman Basha, M.V.Nagabhushanam, D.Nagarjuna Reddy, Brahmaiah Bonthagarala, Comparision of Regulataory Requirements for Generic Drugs Dossier Submission in United States and Canada, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, Issue 6, Vol. 6 , November-December 2016, 1-19.
6. Shaik Salman Basha, S. M. Shakeel, M. V. Nagabhushanam, D. Nagarjuna Reddy, Brahmaiah Bonthagarala, The Assesment of Current Regulatory Guidelines for Biosimilars-A Global Scenario, World Journal of Pharmaceutical Research, ISSN 2277– 7105, volume 6, Issue 1, 351-369
7. www.gabionline.net/reports/generics-market-share-in-europe
8. Review article by santhosh kumar narla, "Marketing Authorization of Human Medicinal products to European Union and European Economic Area." 10(1) 2011.
9. Technical bulletin by arash ghalamkarpour on" Marketing Authorisation Procedures In The European Union-Making The Right Choice". Issue N*33/ December 2009.
10. Marketrealist.com/2016/04/challenges-pharmaceutical-industry-japan/
11. B.Sai Kumari, G.Sai Hanuja, M.V.Nagabhushanam, D.Nagarjuna Reddy, Brahmaiah Bonthagarala, Current Regulatory Requirements for Registration of Medicines, Compilation and Submission of Dossier in Australian Therapeutic goods Administration, International Journal of Advanced Scientific and Technical Research , ISSN 2249-9954, Issue 6 volume 6, November-December 2016, 144-157.
12. G.Sai Hanuja, B.Sai Kumari, M.V.Nagabhushanam, D.Nagarjuna Reddy, Brahmaiah Bonthagarala, Regulatory Requirements for Registration of Generic Drugs in "BRICS" Countries, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, Issue 6, Vol. 6 , November-December 2016, 20-40.