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STREAMLINING REGULATORY COMPLIANCE: CORE DOSSIER DEVELOPMENT FOR EU AND US FILINGS

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ABSTRACT

Pharmaceutical companies are under intense global economic pressure to enhance the value of their assets and expand into new markets. However, they encounter significant challenges such as regulatory delays and submission failures during initial filings. By adopting proactive regulatory strategies, companies can optimize their product portfolios and avoid these issues. Simultaneously, governments are feeling the strain to reduce healthcare expenditures due to aging populations, economic slowdowns, and increasing drug prices. The European Union (EU) and the United States (US) have distinct regional and technical standards for generic drugs. In the US, regulatory information is submitted to the FDA via the Electronic Common Technical Document (eCTD), while the EU operates a centralized system for single applications. Generic medicines must demonstrate pharmaceutical equivalence, conduct bioequivalence studies, and provide clinical evidence supporting safety and efficacy in both markets. These differences must be fully understood to achieve faster drug approvals and ensure patient access to safe and effective generics.

Key words: EU, USA, Generic drugs, CTD, FDA, MRP, Orange book

1. INTRODUCTION

The current global economic climate is placing tremendous pressure on pharmaceutical companies to maximize the value of their assets. Companies with established products want to increase sales by expanding into additional markets to offset impending patent expirations. Confronted with these marketplace challenges, no pharmaceutical company can afford first-round submission failures or other regulatory delays that prevent its products from reaching their targeted markets in a timely fashion. The Common Technical Document (CTD) is submitted based on the requirement of the product approval. The guidance indicates an appropriate format for the data that has been acquired but not what studies are required. This study put forth the differences in registration requirements for generics in the European Union and the United States. It also gives an overview of the administrative documents required for generic drug registration in the Association of Southeast Asian Nations (ASEAN) CTD i.e. ACTD, Eastern European, Commonwealth Independent States, and Latin American countries that follow the CTD format. Bioavailability and Bioequivalence study data are critical in the generic drug approval process. There are several approaches to assessing BA/BE, and each regulatory authority has put forth its regulations/guidance for conducting BA/BE studies required for the approval of generic products. This study also emphasizes the BA/BE concepts, study conditions, designs, and methodology in conducting these studies in the EU and US.Though both countries have very stringent regulations in conducting these studies, the regulatory approaches for conducting BE studies differ in many parameters (dissolution, biowaiver, inclusion-exclusion criteria of subjects, and statistical results). As these differences in regulatory requirements can sometimes act as trade barriers, greatly delaying foreign market access. Hence, it is imperative to be aware of the dossier submission requirements for the EU and US, which can prevent the duplication of studies and speed up the generation of data required by a concerned regulatory authority.

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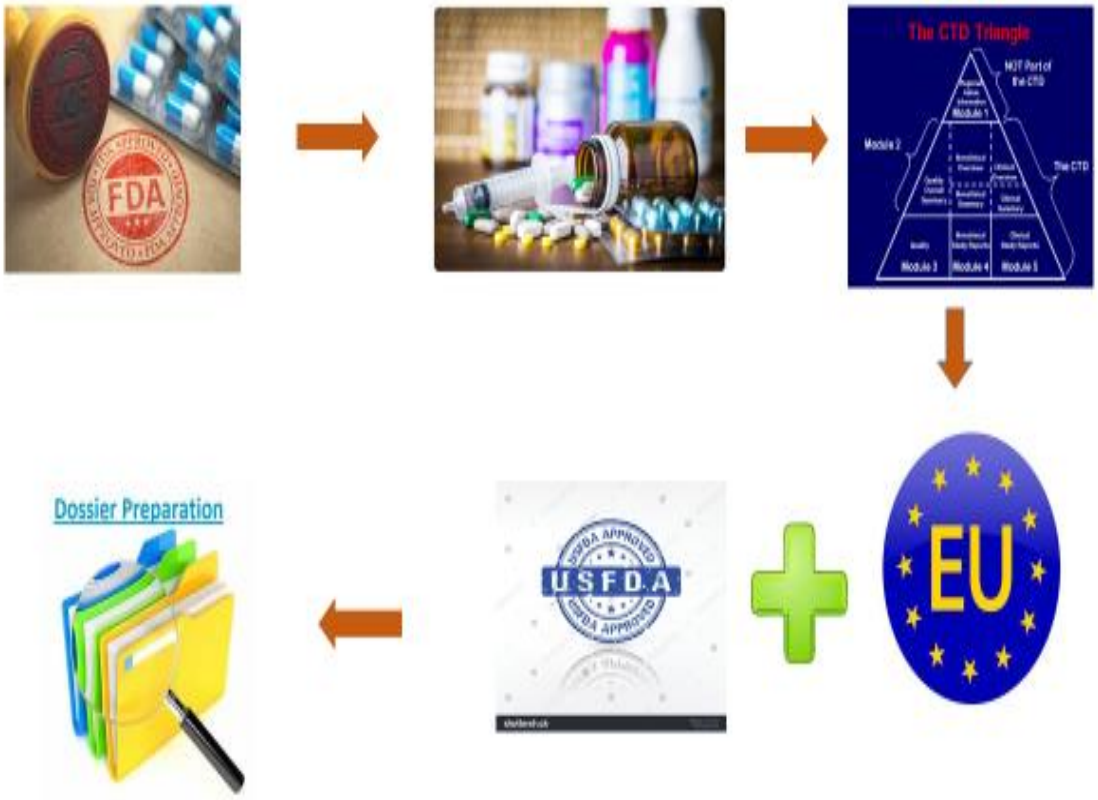

GRAPHICAL ABSTRACT

1.1 Intellectual Property Rights:

The term "Intellectual Property Rights (IPR)" refers to the legal rights granted to protect the creation of the intellect. These rights include Industrial Property Rights (e.g. patents, industrial designs, and trademarks), Copyright (rights of the author or creator), and Related Rights (rights of the performers, producers, and broadcasting organizations).

Role of IPR in the Pharmaceutical Industry:

The pharmaceutical industry is one of the evergreen industries in the world. No matter what happens, whether the economy is at its most stable behavior or in recession mode. Any day a person can fall sick or might require his supplement pills. The products are used 24/7. **Below are the types of IPR involved in the pharmaceutical industry**

• Patents, Industrial designs, Trademarks, Copyright, Trade Secrets.

• A patent is awarded for an invention, which satisfies the criteria of global novelty, non obviousness, and industrial or commercial application. Patents can be granted for products and processes.

Drug Regulatory Affairs[10,11]:

Regulatory Affairs in the Pharmaceutical industry is a profession that acts as the interface between the pharmaceutical industry and Drug Regulatory authorities across the world. It is mainly involved in the registration of the drug products in respective countries before their marketing.

Responsibilities:

• A new drug/generic drug manufactured by a pharmaceutical company just cannot be released into the market for human use.

• Here the Regulatory Affairs Department comes into play.

Generic Drug Product:

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. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. Even more, billions are saved when hospitals use generics. Drug companies must submit an abbreviated new drug application (ANDA) for approval to market a generic product.

The Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act, made ANDAs possible by creating a compromise in the drug industry. Generic drug companies gained greater access to the market for prescription drugs, and innovator companies gained restoration of patent life of their products lost during FDA's approval process.

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Table 1: Comparison of EU and US Market Environment for Generic Medicines

Market Environment for Generic Medicines	EU	US
Generic medicines as % of total Pharmaceutical Market Volume	42%	63%
Basic product patent	Yes (20 yrs.)	Yes (20 yrs.)
Data exclusivity	8+2+ (1) yrs.	5 yrs.
Patent extensions Supplementary protection certificates, etc.	Yes (15 yrs.)	Yes (14 yrs.)
Bolar provision (Right to perform generic R&D before patent expiration)	Yes (but not correctly implemented in all member states)	Yes
Immediate generic competition upon patent expiration	No (due to price & reimbursement procedures in many member states)	Yes
Fees for generic registration	Yes (between 80,000-120,000 Euros)	Yes
Harmonized regulatory and IP requirements	No	Yes

2. METHODOLOGY

Literature review was done mainly on collection of the legislations, concentrating on their generic drug registration procedures in EU and US. The research carried out with the collected data by analyzing the terms of the below parameters: Methodology Each and every study has some patterns and follows certain pathways in order to reach the objective. Thus, the method to be followed plays an important role in determining the outputs as well as the consequences of study.

1. Researching databases, journals, and official regulatory websites to gather scholarly articles, guidelines, and regulatory documents related to generic drug registration.
2. Extracted pertinent information from the literature, analyzed it using a systematic approach, and focused on regulatory frameworks, legislations, and guidelines specific to EU and US requirements.
3. Compares the regulatory requirements in the EU and the US, identifying similarities and differences in approval processes, dossier formats, and administrative documents.
4. The content emphasizes the need to analyze the impact of EU and US regulations on emerging nations and the challenges they face in complying with international standards.
5. The analysis suggests harmonizing generic drug registration procedures by adopting common formats like the Common Technical Document and expanding bioequivalence requirements.

Preparing and Organizing the CTD

In CTD, the display of information should be unambiguous and transparent, which facilitates the review of the basic data and helps a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (EU) and 8.5x11 paper (US). A margin of at least 0.75 inches from the bound edge of the printed page is required to prevent information from being obscured and to place the paper in a binder. Narrative text is submitted in Times New Roman 12-point font. Generally, font sizes 9 to 10 points are considered acceptable in tables. Ten-point fonts are recommended for footnotes. Acronyms and abbreviations should be defined the first time they are used in each module.

The CTD is divided into five modules:

• Module 1 - Administrative and prescribing information
• Module 2 - Overview and summary of modules 3 to
• Module 3 - Quality (Pharmaceutical documentation)
• Module 4 - Nonclinical document safety (toxicology studies)
• Module 5 - Clinical document efficacy (Clinical studies)

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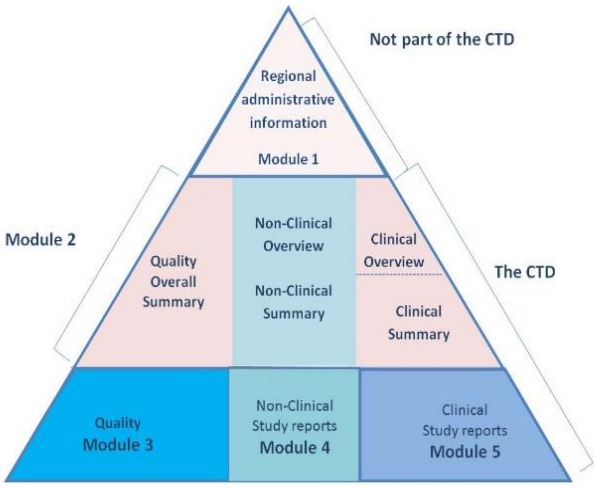

Fig.1 CTD dossier

Module 1 Administrative and prescribing Information:

This module contains administrative documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module is specified by the relevant regulatory authority.

Module 2 Common Technical Document Summaries:

Module 2 begins with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the introduction should not exceed on page.

Module 2 contains 7 sections in the following order:

1. CTD Table of Contents
2. CTD Introduction
3. Quality Overall Summary
4. Non-clinical Overview
5. Clinical Overview
6. Non-clinical Written and Tabulated Summaries
7. Clinical Summary.

As Module 2 contains information from the Quality, Efficacy and Safety sections of the CTD, the organization of the individual Module 2 summaries is discussed in three separate documents:

• M4Q: The CTD - Quality
• M4S: The CTD - Safety
• M4E: The CTD - Efficacy.

Module 3 Quality

Information on Quality is presented in the structured format as described in the guidance, M4Q.

Module 4 Non-clinical Study Reports

The Nonclinical Study Reports is presented in the order as described in the guidance, M4S.

Module 5 Clinical Study Reports

The human study reports and related information are presented in the order as described in the guidance M4E.

DRUG APPROVAL PROCEDURES IN EU

Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approval procedures. The marketing authorization procedure is applicable to European economic area (EEA) which includes 27 EU member states and the three EEA EFTA states (Iceland, Liechtenstein, and Norway). Hence, EEA constitutes a total of 30 countries. The primary purpose of the rules governing medicinal products is to safeguard public health. The objective of the pharmaceutical legislation of the European Community is to protect public health and to monitor the free movement of medicinal products. The regulation of medicinal products is governed in the EU/EEA by directive 2001/81/EC relating to medicinal products (the Directive). The EMA is a decentralized body of the European Union with headquarters in London. The main scientific work of the agency is conducted by the six scientific committees (CHMP, CVMP, COMP, HMPC, PDCO, CAT) and members of all EU and EEA-EFTA states to place a medicinal on the market in the European Economic Area (EEA) a Marketing Authorization have been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorization) or when an authorization has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a community authorization).

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Marketing authorization procedures in EU

- Centralized Procedure (CP)
- National Procedure (NP)
- Mutual Recognition Procedure (MRP)
- Decentralized Procedure (DCP)

DRUG APPROVAL PROCEDURE IN US (ANDA)

Hatch -- Waxman Act

In 1984, Hatch- Waxman Amendments to Federal Food, Drug and Cosmetic Act (FD&C Act) came and it was considered one of the most successful pieces of legislation ever passed and created the generic drug industry (Drug Price Competition and Patent Term Restoration Act of 1984). The act required FDA to publish received patent information and began printing the patent listings in a volume entitled Approved Drug Products with Therapeutic Equivalence – Orange Book. Under this act four types of certifications are possible.

They are

• Paragraph I certification states that the application does not cite patented Information previously listed in the Orange Book

• Paragraph II certification states that the patented information cited in the Application, and listed in the Orange Book, has expired.

• Paragraph III certification states the date on which the listed Orange Book. Patents for the information cited in the ANDA application will expire

• Paragraph IV certification attests to the manufacturer‘s opinion that the listed Orange Book patent is invalid, or will not be infringed by the use, manufacture, or sale of the new drug for which the ANDA is submitted.

Generic manufacturers filing Paragraph IV certifications were required to provide notice to the relevant pioneer drug companies and patent holders explaining why the listed patents cited in the ANDA were either invalid or not infringed by the ANDA Submission. At the same time an NDA or patent holder could file a valid infringement suit within 45 days of receipt of a Paragraph IV notice. In addition, the Act created an automatic thirty-month window in which the patent infringement dispute could be litigated without risk of generic entry into the market. The effective date of FDA approval was delayed until a judicial ruling on the infringement of validity of the patent, or until thirty months have elapsed, whichever occurred sooner.

The Act provided additional incentives to the generic companies in the form of a marketing exclusivity provision. The first company that filed an ANDA with a Paragraph IV certification as to a particular patent or patents was granted a 180-day monopoly by the FDA. During this time, the FDA would not give any other ANDA approval for subsequent generics for 180 days. Thus, this act made following three important provisions: I) it provided for the extension of the term of one existing patent for innovator drugs; II) it made provisions for the marketing of generics of patented drugs on the day after patent expiry; and III) it provided opportunities to challenge the validity of patents issued to innovator drug companies

Filling Review of ANDA

The ANDA process begins when an applicant submits an ANDA to the OGD. The document room staff processes the ANDA, assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA Checklist. Within the first 60 days following the submission of an ANDA, a filling review is completed. The Regulatory Support Branch (RSB) is responsible for the filling review. The RSB ensures that the ANDAs contain the information necessary to merit a technical review. To determine whether an application is acceptable for filling, an RSB project manager (RPM) compares the contents of each section of Application against a list of regulatory requirements.

Bioequivalence Review Process

After an ANDA is accepted for filing by the RSB, the bioequivalence section is assigned to the Division of Bioequivalence (DBE) to review. The bioequivalence review process establishes bioequivalence between a proposed generic drug and the RLD. Bioequivalence is established when the ratio of the means of the test product compared to the reference product (T = R) of the pharmacokinetic parameters for rate (Cmax) and extent of absorption (AUC) of log transformed data meet the 90% confidence intervals of 80--125%. The BPMs request and track inspections of the clinical and analytical sites through the Division of Scientific Investigations (DSI).

The clinical and analytical sites are inspected for two reasons: (1) to verify the quality and integrity of the scientific data submitted in bioequivalence studies and (2) to ensure that the rights and welfare of human subjects participating in the

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studies are protected in accordance with the regulations (21 CFR 312, 320, 50, and 56). If any issue arises during the review process the BPM initiates a teleconference with the applicant. The applicant‘s response to the teleconference is labeled as a Bioequivalence Telephone Amendment ‘‘When a review contains numerous deficiencies and requires more than 10 days to resolve, a deficiency letter is issued to applicant. Once the bioequivalence review is completed and all bioequivalence requirements are addressed, and all deficiencies are fulfilled, the DBE forwards an acceptable letter that states that there are no further questions at this time. The bioequivalence review is then forwarded to the APM.

Chemistry Review Process

After an ANDA has been accepted for filing by the RSB, the Chemistry, Manufacturing and Controls (CMC) section of the application is assigned to the appropriate Chemistry Division and Team, based on the therapeutic category of the drug product. The Chemistry Divisions review the CMC section of ANDAs, Drug Master Files, Supplemental ANDAs, Annual Reports, and Controlled Correspondence. The goal of the chemistry review process is to assure that the generic drug will be manufactured in a reproducible manner under controlled conditions. The chemistry reviewer drafts a primary review that is forwarded to the team leader for secondary review. Once the team resolves the issues internally, the review is finalized and signed by the team leader, primary reviewer and APM.

Module 1 Administrative Information and Prescribing Information EU31

The content of Module 1 is defined by the European Commission in consultation with the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products and interested parties. It includes:

1.0 Cover Letter

1.1 Comprehensive Table of Contents

1.2 Application Form

1.3 Product Information

1.3.1 Smpc, Labeling and Package Leaflets

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

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 Authorization

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

1.10 Information relating to Pediatric

Responses to Questions

Additional Data

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1.0 Cover Letter

Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies can include comparisons between: The drug product used in clinical studies supporting effectiveness and the to- be-marketed drug product. The drug product used in clinical studies supporting effectiveness and the drug product used in stability batches Similar drug products from different manufacturers.

3. CONCLUSION

Table 2: Comparison of Regulatory Requirement of EU and US

Regulatory Requirement	European Union	United States
Administrative information		
Application	Marketing Authorization Application (MAA)	Abbreviated New Drug Application (ANDA)(505j)
Type of drug filling	Centralized procedure, National procedure, MRP, Decentralized procedure.	No such requirement.
Approval timeline	12 months	18 months
Requirement for application	Based on Data\Market exclusivity	Based on Patent certification (Paragraph I, II, III, IV)
Agent authorization	Not required	Required
Debarment certification	Not required	Required
Pharmacovigilance	Required	Not required
Control of Drug Product		
Manufacturer FEI number	Not required	Required
Identification of color	Required	Not required
Number of batches required during submission	Two batches	Single batch
Stability		
Selection of Reference drug	With reference to marketing authorization is or has been granted in the Union	With reference to Orange book listed patent.
CRO	Audited by MHRA	Audited by FDA
Dosage strength	No such requirement	BA and BE are conducted on highest strength.
Body Mass Index (BMI)	Between 18.5 and 30 kg/m^2	Not addressed
Type of Study		
Fed study	Required if the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food interaction or else only Fasting is sufficient.	Not required in the following cases: 1) High solubility and high permeability (BCS Class I) drug product; or 2) RLD label stating that the product should be taken only on an empty stomach; or 3) When the RLD label does not make any statements about the effect of food on absorption or administration.

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Fasting Study	Fast atleast 8 h prior to administration and administer the drug product with 150 mL of water	Fast atleast 10 h and administer the drug product with 240 mL (8 fluid ounces) of water.
Retention of Samples	Retain for 1 year or 2 years after completion of the trial or until approval.	Retain samples for 5 years.
Composition of meal under fed condition	According to recommendation in the SmPC of reference drug or Standardized high fat high calorie meal	As OGD recommendation
Wash out period	Adequate. In steady state atleast 3 times terminal half lives.	More than 5 half-lives.
Reserve Sample	No such requirement	5 times the sample required for analysis
Dissolution		
Use of surfactant	Strictly discouraged.	Recommends appropriate concentration.
Sampling time points	A minimum of three time points (zero excluded).	Collected at sufficient number of intervals.
Sampling criteria		12 to 18 samples, including a Predose sample, are collected per subject per dose. Continue the sampling for 3 or more terminal half-lives.
Two stage design to demonstrate BE	Recommended	Not addressed
Regional Information		
Regional information	Process validation scheme for drug product Certificate of suitability TSE/BSE certificates of suitability are to be attached	Executed batch record Method validation package Comparability protocol
Labeling Requirement		
National Drug Code (NDC)	Each member state has specific code.	Required (10 digit)
Prescription status	Rx	Prescription Only Medicine (POM)
Side by side (Annotated) Comparison	Not required	required
Readability testing	required	Not required
Braille	required	Not required
Labels	Vials/carton/SPC	Vials/cartons/PIL
Information on reimbursement or a pictogram presented in a —Blue box	Required	No such requirement.

The International Council for Harmonisation (ICH) is a global initiative that aims to achieve greater harmonization in the interpretation and application of technical guidelines for pharmaceuticals. It aims to streamline drug development and registration processes, promote public health, minimize duplication of clinical trials, and ensure safety and effectiveness. ICH's objectives include efficiency, public health, preventing duplication of clinical trials, and

harmonization. Generic drugs play a crucial role in the pharmaceutical market, accounting for over 50% of the market. ICH aims to develop and enhance guidelines specifically for generic drugs, addressing areas where internationally harmonized guidance is lacking. The Common Technical Document (CTD) and Electronic Common Technical Document (eCTD) are essential frameworks for organizing and submitting comprehensive regulatory dossiers for drug approvals. The CTD is a standardized format for presenting data in regulatory submissions related to human pharmaceutical products, designed to provide a common structure across different regions (Europe, USA, and Japan). It is divided into five main modules: administrative information and prescribing information, summaries of quality, safety, and efficacy data, quality data (chemistry, manufacturing, and controls), nonclinical study reports, and clinical study reports. The CTD facilitates efficient communication between regulatory authorities and pharmaceutical companies, streamlining the review process. The eCTD is the standard format for submitting applications, amendments, supplements, and reports to regulatory agencies such as the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). The European Union (EU) has two main routes for drug approval: centralized and national. The centralized procedure involves pharmaceutical companies submitting a single marketing authorisation application to the European Medicines Agency (EMA), which assesses the application scientifically and provides a recommendation on whether the medicine should be marketed. Once granted, the EMA's recommendation is legally binding and valid in all EU Member States and the European Economic Area (EEA). The procedure is compulsory for medicines containing new active substances, biotechnology-derived medicines, advanced therapy medicines, orphan medicines, and veterinary medicines.

The national authorization procedures involve simultaneous authorisation in multiple EU Member States and mutual recognition of marketing authorizations. These procedures aim to standardize the approval process across member states while considering therapeutic efficacy and safety. The International Council for Harmonisation (ICH) provides specific information on drug substances and products for each region. The US FDA plays a crucial role in drug regulation, ensuring safety, efficacy, and quality. Generic drug manufacturers submit an ANDA to demonstrate bioequivalence to the reference listed drug (RLD).

The European Union (EMA) oversees drug regulation across EU member states, granting centralized marketing authorizations for certain drugs. Pharmaceutical companies in emerging nations must submit several administrative documents for drug registration, including application forms, cover letters, Power of Attorney (PoA), product information and labeling, authorization letter for local agents/distributors, GMP (Good Manufacturing Practice) certificate, Free Sale Certificate (FSC), Certificate of Pharmaceutical Product (CPP), and product samples. These documents are crucial for the regulatory process, ensuring the drug's safety, efficacy, and consistency. The application forms provide essential information about the drug, its intended use, and the company. A PoA allows a local representative to act on behalf of the pharmaceutical company. The CPP verifies the product's approval for sale and meets quality standards.

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