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Navigating Regulatory Landscapes: A Comprehensive Exploration of New Drug Approval Dossiers in the Complex Markets of the US, EU, and India

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ABSTRACT:

The Pharmaceutical Regulatory Affairs (PRA) division plays a crucial role within a pharmaceutical company by effectively steering the company's Research and Development (R&D) initiatives towards market success. In the current context, various countries possess distinct regulatory prerequisites for granting approval to a novel pharmaceutical product. Creating a cohesive regulatory plan for the submission of a new drug product's marketing authorization application (MAA), which could be applied across multiple countries through a single dossier, presents significant challenges.
Therefore, the knowledge of exact and detailed regulatory requirements for MAA of each country should be known to establish a suitable regulatory strategy. The creation of the Common Technical Document (CTD) was driven by the goal of establishing a uniform template for technical documentation, streamlining the process of compiling registration applications for human pharmaceuticals. This standardization also aimed to simplify the preparation of electronic submissions while reducing the associated time and resource requirements.
The development of a novel pharmaceutical necessitates extensive research across multiple domains, including chemistry, manufacturing practices, quality controls, preclinical sciences, and rigorous clinical trials. Regulatory agencies worldwide assign the task of assessing the research data to drug reviewers, who determine whether they substantiate the public health-serving attributes of safety, efficacy, and quality control for new pharmaceutical products. Each nation maintains an independent regulatory body tasked with enforcing rules and regulations, as well as issuing guidelines to oversee the marketing of pharmaceuticals. This work focuses on drug approval process and new drug applications in different countries like USA, Europe and India.

Keywords: Nda, Pra, Ctd, Maa, Usfda, Ema, Cdsco, Dcgi.

INTRODUCTION:

A new drug pertains to a pharmaceutical product that has not been verified as safe and effective by qualified experts under the specified conditions indicated, recommended, or suggested on the label. This can encompass either a novel chemical composition or an existing medication prescribed for a new application.
Guidelines that should be followed for the regulation of new drugs in Challenging Markets are

1. USFDA:

Established in 1930 as part of the U.S. Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA) governs commodities contributing to approximately 25% of the gross national product of the United States.

As part of the U.S. Department of Health and Human Services (DHHS), the U.S. Food and Drug Administration (FDA) is responsible for ensuring the safety oversight of:

- Various food products
- Pharmaceuticals
- Vaccinations
- Blood-related products
- Medical devices
- Dietary supplements

- Biomedical products of a biological nature
- Devices that emit radiation
- Veterinary products
- Cosmetic items

Situated in White Oak, Maryland, is the headquarters of the FDA.
Moreover, the organization operates a system of 223 regional offices and 13 research facilities distributed across all 50 states, along with the United States Virgin Islands and Puerto Rico. Beginning in 2008, the FDA also initiated the establishment of branches in international locations, such as China, India, Costa Rica, Chile, Belgium, and the United Kingdom.

2. EU:
The upcoming enactment of the Clinical Trial Regulation is poised to bring about a significant change in the way clinical trials are conducted in the European Union (EU).

The Regulation standardizes the evaluation and oversight procedures for clinical trials across the EU by means of a Clinical Trials Information System (formerly referred to as the EU clinical trial portal and database). The European Medicines Agency (EMA), in cooperation with the Member States and the European Commission, will create and oversee the information system.

Clinical Trial Regulation EU No. 536/2014 aims to establish a conducive environment for conducting clinical trials within the EU, upholding the utmost safety standards for participants and enhancing the transparency of trial information. The Regulation will necessitate:

- Consistent rules for the execution of clinical trials throughout the EU will be in place,
- and comprehensive information about the approval, execution, and results of each clinical trial conducted within the EU will be available to the public.

This step will improve the efficiency of all trials conducted in Europe, with the greatest benefits seen in trials spanning multiple Member States. The aim is to foster innovation and research while avoiding unnecessary duplication of clinical trials and the repetition of unsuccessful ones.

3. CDSCO:
The Central Drug Control Standard Organization serves as the primary Drug Authority responsible for carrying out tasks delegated to the central government in accordance with the Drugs and Cosmetics Act.
• CDSCO oversees 6 regional offices, 4 subsidiary regional offices, 13 harbor offices, and manages 7 laboratories. The CDSCO office regulates the clinical trials via its central office at New Delhi and four zonal offices situated at Mumbai, Chennai, Kolkata and Ghaziabad.

These zonal offices work in close collaboration with the state offices to bring about uniform enforcement of the regulations imposed by the central government.
Major Functions of CDSCO:
• Supervision of drug imports and the authorization process for new drugs.
• Clinical trials, DCC & DTAB approval of certain licenses as central license approving authority is exercised by CDSCO headquarters.
In India, the Central Drugs Standard Control Organization (CDSCO) functions under the jurisdiction of the Ministry of Health and Family Welfare, serves as the primary entity responsible for formulating regulatory protocols and benchmarks related to drugs, cosmetics, diagnostics, and devices. By revising acts and regulations, it provides regulatory guidance and oversees the process of approving new drugs. The primary aim is to standardize clinical research practices and introduce safer pharmaceuticals to the Indian market.

New drug applications (NDAs):
A New Drug Application (NDA) can only be filed once the drug has completed all three clinical trial phases. The submission must include thorough data from both animal and human studies, data analysis, drug pharmacokinetics, manufacturing specifics, and the proposed labeling information. In the Center for Drug Evaluation and Research, a group of scientists examines preclinical and clinical reports, along with conducting a risk-benefit analysis to ensure that the product's positive effects outweigh any possible negative effects.

After clinical studies confirm the new drug's safety and effectiveness while minimizing patient risks, the manufacturer goes ahead with submitting a New Drug Application (NDA).

This NDA serves as the formal request for manufacturing and selling the drug within the United States.
Typically, NDA approval is obtained within an average timeframe of two years. However, this process can span anywhere from two months to several years to reach completion. Following NDA approval, the pioneering company gains authorization to market the drug and concurrently engages in Phase IV trials. During this stage, exploration involves new domains, applications, or populations, as well as the study of long-term impacts and the diverse responses of participants to varying dosages.

To obtain approval for the marketing of a new drug in the United States, a New Drug Application (NDA) is submitted. The NDA includes information from the IND, as well as the results of clinical trials confirming the safety and efficacy of the drug. The FDA commences the review process approximately two months after the submission of the NDA. The NDA comprises the Contents and Format, with two copies of the application submitted:

a. Archival copy
b. Review copy
a. Archival Copy: This edition serves as a reference resource for FDA reviewers to retrieve information that is not present in the review copy. It includes tables and duplicates of clinical study case report forms. It contains the following elements:
1. Application Form FDA 356
2. Index
3. Summary
4. Technical Sections: Further categorized as
- Section for Chemistry, Manufacturing, and Controls
- Section for Non-clinical Pharmacology and Toxicology
- Section for Human Pharmacokinetics and Bioavailability
- Microbiology Section
- Clinical Data Section
- Statistical Section
- Pediatric Use Section

5. Samples and Labeling
6. Case Report Forms
b. Review Copy: Each specific technical section is separately compiled in its assigned folder. Each technical section should include the following components:
1. Index
2. Duplicate of FDA Form 356h
3. Replication of the cover letter
4. Authorization letters
5. Reproduction of the application summary.
The FDA can choose to conduct meetings with the sponsor on two separate occasions: one after the Phase 2 clinical trials are completed, and another before the submission of an NDA, which is referred to as a pre-NDA meeting. During these meetings, the review team will evaluate the study results to decide whether to approve the application.

Post marketing (Phase IV) Studies:
As part of the approval process, the FDA may obtain commitments from the sponsor to do additional Phase 4 studies after the product is marketed. However, the FDA cannot enforce compliance. The FDA also monitors adverse events through an adverse event surveillance program.

The request for authorization entails comprehensive details encompassing:
1. Chemical and pharmaceutical information,
2. Data on animal pharmacology,
3. Data on animal toxicology,
4. Data on human clinical pharmacology,
5. Regulatory status in other nations,
6. Comprehensive prescribing information as an integral aspect of new drug approval for marketing,
7. Thorough testing protocols for quality control examination, and
8. A comprehensive impurity profile and specifications for product release.

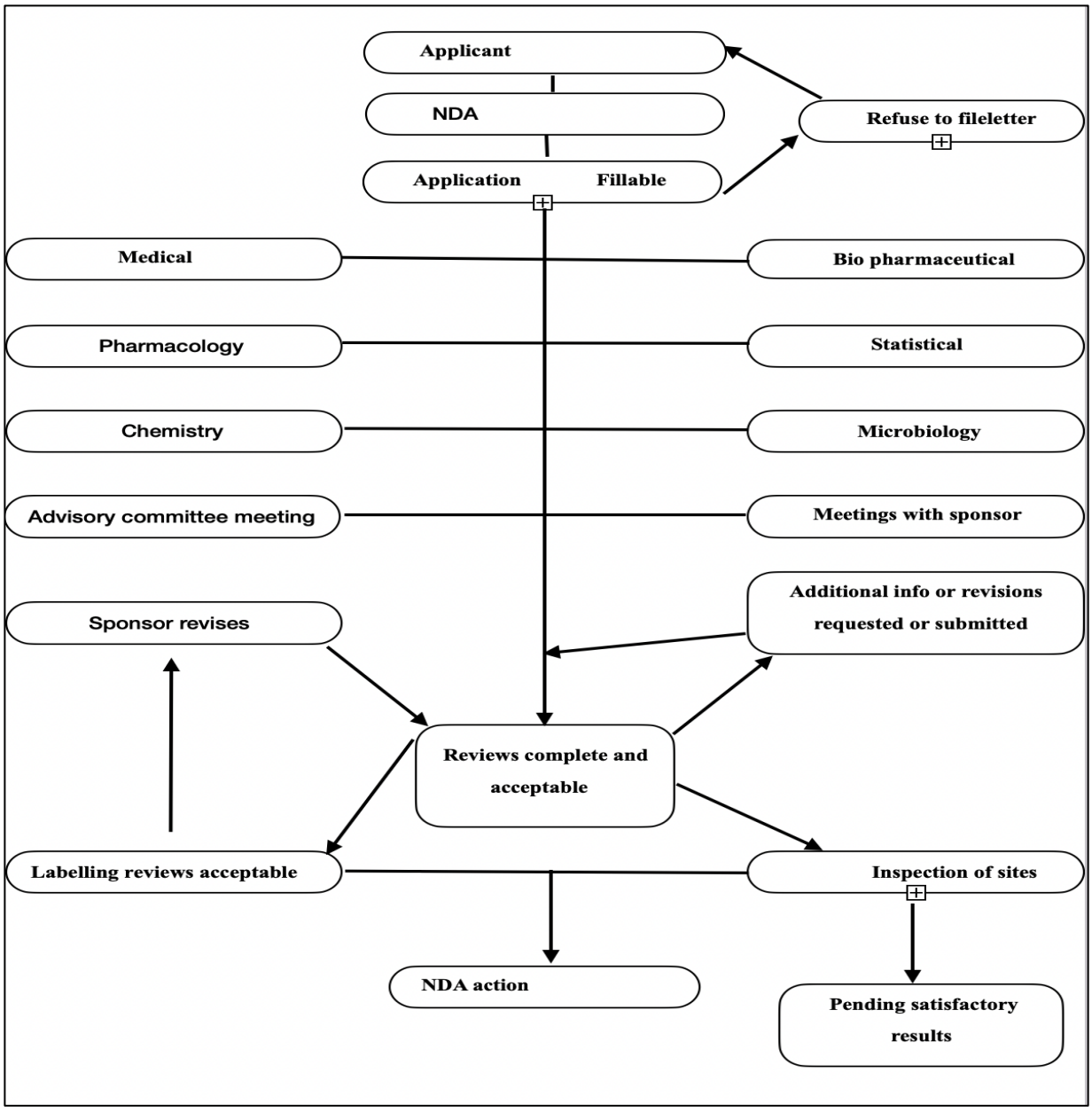

Figure 1: Flow chart of New Drug Application

RESULTS:

Table 1: Principle differences between the US, EU & INDIA:

Requirements	US	EU	INDIA
Registration process	One registration process	Multiple registration process 1. Centralized (European community) 2. Decentralized (At least 2 member states) 3. Mutual recognition (At least 2 members states) 4. National (1 member state)	One registration process
Agency	One agency USFDA	Multiple agencies 1. EMEA 2. CHMP 3. National Health agencies	One agency DCGI
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: 1. Minor changes 2. Moderate changes 3. Major changes	Post-variation in the approved drugs: 1. Type 1A variation 2. Type 1B variation 3. Type 2 variation	Post approval changes: 1. Major quality changes 2. Moderate quality changes

Table-2: Administrative Requirements:

Requirements	US	EU	INDIA
Application	ANDA/NDA	MAA	MAA
Department Classification	Required	Not required	Not required
Number of copies	3	1	1
Approval timeline	~18 Months	eCTD	Paper
Fees	Under $2 Million- NDA Application $51,520-ANDA Application	National fee (including hybrid applications)	50,000 INR
Presentation	ECTD & Paper	eCTD	Paper

Comparative study of Dossier submission of a drug product Administrative. This involves the administrative requirements like application, number of copies, fees and type of presentation required mentioned in Table 2.

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
Color identification	Not required	Required	Required
Water Content	Required	Not required	Required

Table-4: Manufacturing and control requirements:

Requirements	US	EU	INDIA
Number of batches	1	3	1
Packing	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 1lakh units whichever is higher	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 Batch (if API Stable) 3 Primary Batches (if API Unstable)	2 Pilot Batch/Production Scale (if API Stable) 3 Primary Batches (if API unstable)
Condition: long term stability, Accelerated stability	Long Term: 250C/60%RH Accelerated: 40oC/75%RH (0,3,6 months) Intermediate: 30oC/65%RH	Long Term: 25oC/60%RH Accelerated: 40oC/75%RH (0,3,6 months); Intermediate: 30oC/65%RH	Long Term: 30Oc/70%RH Accelerated: 40oC/75%RH (0,3,6 months)
Minimum 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	Inverted & Upright
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	Audited by CDSCO
Reserve Sample	5 times the sample required for analysis	No such requirements	-
Fasted/Fed	Must be as per OGD recommendation	No such requirements	As CDSCO recommendation
Retention of Samples	5 Years from date of filing the application	No such requirements	3 years from date of filing the application
BE study for generic drugs	Against US RLD in any country. Refer to 'BE recommendation' in FDA site for guidance.	Against EU reference products (ERP) in any country.	Against US/EU/Australia RLD in any country except Thailand, where BE to be done locally against local reference product.

DISCUSSION:

Broadly, the process of drug approval typically comprises two primary stages: Seeking approval to carry out clinical trials and requesting authorization from the regulatory body to market the drug. While there are similarities in certain aspects, the process for approving new drugs varies among different countries.

Across many countries, sponsors typically initiate the process by applying to conduct clinical trials. Following approval by the regulatory authority, the applicant proceeds to conduct clinical studies. Afterward, an additional application is sent to the regulatory agency to request marketing authorization for the drug.

While the information submitted to regulatory authorities regarding the quality, security, and effectiveness of drugs remains uniform across all countries, discrepancies emerge in relation to the timelines, fees, and review processes associated with clinical trials and applications for marketing authorization.

In pursuit of harmonization, the International Conference on Harmonization (ICH) has made substantial endeavors to offer recommendations with the goal of ensuring uniform understanding and implementation of technical guidelines and prerequisites.

In the pursuit of harmonization, the International Conference on Harmonization (ICH) has made substantial efforts to offer recommendations that are designed to promote a uniform interpretation and application of technical guidelines and requirements.

The International Conference on Harmonization (ICH) process has resulted in the creation of Common Technical Document (CTD) guidelines, which have been embraced by nations like Japan, Canada, the European Union, the United States, among others. As a result, India also conforms to these standards.

The regulatory agency for INDIA and US is a single agency i.e., CDSCO and USFDA respectively, whereas in EU, there are three regulatory agencies, they are EMEA, CHMP and NATIONAL HEALTH AGENCY. Europe also has multiple regulatory procedures when compared to US and INDIA. The approval time in all the countries is almost the same i.e., 12 to 18 months (about 1 and a half years). The fee for the new drug approval in US is very high when compared to EUROPE and INDIA.

CONCLUSION:

The new drug approval processes of various countries are similar and differ in some aspects. Initially, the applicant submits an application to carry out a clinical trial. Following approval from the governing body, the applicant proceeds with the clinical studies and subsequently lodges an application with the same regulatory body to obtain marketing authorization for the drug.

Across all nations, the information submitted to regulatory authorities concerning the drug's quality, safety, and efficacy remains comparable. However, variations emerge in terms of the timeframes, fees, and review procedures Related to clinical trials and requests for marketing authorization.

In the quest for harmonization, the International Conference on Harmonization (ICH) has taken substantial steps to offer recommendations with the goal of ensuring a uniform understanding and implementation of technical guidelines and prerequisites.

Ultimately, this action will result in a decrease in the need to duplicate efforts made during the research and development of new pharmaceuticals. Therefore, the establishment of global-level harmonization for drug approval procedures, whether through ICH or WHO, becomes a feasible possibility.

The approval of drugs in India, Europe, and the United States carries immense global importance. The primary goal of the regulations governing medicinal products in these areas is to safeguard public health. It falls upon public regulatory authorities to ensure that pharmaceutical companies comply with these regulations. Various legislations mandate the development, testing, trial, and manufacturing of drugs in alignment with established guidelines, ensuring the safety and well-being of patients.

In this study, we have examined both the commonalities and distinctions within the drug approval processes, along with the documentation and CTD specifications essential for submission to drug regulatory authorities in Europe, the USA, and India. Additionally, we investigated the submission and workflow aspects pertaining to bioavailability and bioequivalence studies. The implementation of CTD establishes a standardized structure for technical documentation, resulting in a substantial reduction in the time and resources needed to prepare applications for human pharmaceutical registration. Moreover, it facilitates the creation of electronic submissions and enhances the seamless exchange of regulatory information among different regulatory authorities.

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Conflict of Interest:
The Authors declare no conflict of interest

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