ABSTRACT

Regulatory Agencies or Drug Regulatory Agencies in a pharmaceutical industry acts as the operational interface between the pharmaceutical companies and drug regulatory agencies or authorities that are to be workforce for regulatory purpose across the world. These agencies look after the regulatory requirement and setup standards and procedural requirements for pharmaceutical products and API manufacturing. These agencies are involved in regulatory operations based on standard procedures which have specific operation procedures called as SOP’s that are known as Standard Operating Procedures. The regulatory agencies sets standards based on clinical requirements and obtained data for safety of drug and drug products as a pharmaceutical product/API. The important roles of such agencies and authorities are based on evaluation of clinical safety data and to ensure protection of human health ensuring all the parameter such as: safety, efficacy and quality of drugs ensuring appropriateness and accuracy of products information.

KEYWORDS: Regulatory Agencies, U.S. FDA. MHRA.

1. INTRODUCTION

Regulatory Agencies or Drug Regulatory Agencies in a pharmaceutical industry have a regulatory interface on Pharmaceutical products for human use. There are various regulatory agencies across the world carrying out operational functions based on their regulation as administrative, chemistry, pre-clinical and clinical studies with the permission granted by the regulatory agencies of a country with a view to support its marketing/approval on the ‘Registration’, ‘Marketing Authorization.’ Or the product licensing.’ These all related
regulatory submission are based on ‘Regulatory Dossier’ of the pharmaceutical product that is designed based on contents that is related to technical data (administrative, quality, non-clinical and clinical) study of a pharmaceutical product to be approved/registered/marketed in a country. Such applications are called as New Drug Application. (NDA) in the USA or Marketing Authorization Application (MAA) in the European Union (EU), or simply it is called as registration dossier.

A registration dossier contains all the details and key terminologies regarding to quality, efficacy and safety of a pharmaceutical product that are intended for medical use. Thus it is a document that produces details containing various pharmaceutically important aspects of the new drug or investigational drug. This is all involved in a process to submission by which an organization/sponsor/ innovator uses a regulatory process to get authorization to launch its pharmaceutically approved drug in the market. This is called a drug approval process. Drug approval process constitute of various stages, involving:

1. Application to conduct clinical trials,
2. Conducting Clinical trials,
3. Filing of registration dossier or a new drug application (NDA).
4. Post marketing surveillance/ study.

Regulatory authority enforce rules and regulations based in a form of guidelines which include parameters based on safety, efficacy and quality of drugs ensuring appropriateness and accuracy of product information.

---

**Figure 1: Regulatory Process.**
The crucial role that regulatory agencies play is based on data, safety data that is obtained out from studies. Depending on this safety data that is obtained it is decided whether to pass the IP or retain it.

Significantly, regulatory agencies ensure safety of food and drug products. One such agency is U.S. FDA.

2. Role of a Pharmacy Professional in Regulatory
The significant role of a pharmacy professional is to act as a liaison with regulatory agencies involve in data monitoring, preparation of scientifically valid and organized:
1. NDA
2. ANDA
3. INDA
4. MAA
5. DMF

For submission to authorities while data monitoring adjudge a key role and the other vital role is to ensure adherence and compliance with all the applicable cGMP, ICH, GCP, GLP guidelines and regulations, providing all expertise regulatory requirements.

2.1. Some of the commonly used Abbreviations in Regulatory procedures are
1. NDA-New Drug Application.
2. ANDA-Abbreviated New Drug Application.
4. DMF-Drug Master File.
5. ASMF-Active Substance Master File.
7. CEP-Certificate of Suitability to the monographs of the European Pharmacopoeia.
8. CTD-Common Technical Documents for the registration of pharmaceuticals for human use.
9. AP-Applications Part.
10. RP-Restricted Part.
11. OP-Open Part.
12. CP-Closed Part.
13. NME-New Molecular Entity.
ICH brings together the guidelines from regulatory authorities of Europe, Japan and the United States, from the Industry experts too for scientific discussion on technical aspects of pharmaceutical product registration. Thus ICH brings all together regulatory requirements in the form of guidelines.

4. Technical Terms and Discussion
Federal and State Regulatory Requirements
1. Investigational New Drug (IND) application
It is an application which is filled with FDA to get approval for legally testing an experimental drug or IP for its development.

2. New Drug Application
The NDA is the dossier through which drug sponsors formally propose that the FDA approve a new pharmaceutical drug for sale and marketing in the U.S. The data gathered during the preclinical studies and the clinical trial data of an Investigational new drug becomes a part of the NDA which has animal studies involved in it and the clinical safety evaluation.
In simple words, ‘It is an application which is filed with FDA to market a new Pharmaceutical for sale in USA.’

3. **Abbreviated New Drug Application (ANDA)**

It is an application filed with FDA for a U.S. Generic drug approval for an existing licensed medication or approved drug. In simple words. ‘It is an application for the approval of Generic Drugs.’

4. **A DMF-Drug Master File**

A DMF or Drug Master File is a submission to the food and drug administration (FDA) that may be used to provide confidential detailed information about facilities, processes or articles used in the manufacturing, processing, packaging and storing of one or more API or IP.

The important facts regarding DMFs is that it is submitted to FDA to provide confidential information. Its Submission is not required by law or regulations. It is neither approved nor disapproved. It is filed with FDA to support NDA, IND, ANDA another DMF or amendments and supplements to any of these. It is provided for in the 21 CFR (code of Federal Regulations) 314.420.

It is not required when applicant reference its own information.

5. **Type of DMF’s**

Type I: Manufacturing site facilities, operating procedures and personnel (no longer accepted by FDA).

Type II: Drug Substance, Intermediate and material used in their preparation or drug product.

Type III: Packaging Material.

Type IV: Excipient, Colorant, Flavor, Essence or Material used in their Preparation. Type V: FDA Accepted Reference information (FDA discourages its use).

6. **505 (b) (2) application**

A 505 (b) (2) application is a type of NDA for which one or more investigations are relied on by applicant for approval were not conducted by or for applicant and for which applicant has not obtained a right of reference.

i. What are the kind of application can be submitted as a 505 (b) (2) application?

New chemical entity (NCE)/ new molecular entity (NME) changes to previously approved drugs.
ii. What are the examples of changes to approved drug products for which 505 (b) (2) application should be submitted?
Change in dosage form.
Change in strength.
Change in route of administration.
Substitution of an active ingredient in a formulation product. Change in formulation.
Change in dosing regimen.
Change in active ingredient, New Combination Product, New Indication. Change from prescription indication to OTC indication.
Naturally derived or recombinant active ingredient Bioequivalence.

7. Chemical Classification codes for NDA
1. New molecular entity (NME).
2. New ester, new salt, or other non-covalent derivative.
3. New Formulation.
4. New Combination.
5. New Manufacturer.
7. Drug already marketed but without an approval NDA.
8. OTC (Over the counter) Switch.

7. Differences between NDA and 505 (b) (2) application
New drug application (NDA) 505 (b) (2) application
1. All investigations relied on by application for approval were conducted by/for applicant and for which applicant has right of reference one or more investigation relied on by applicant for approval were not conducted by/for applicant and for which applicant has not obtained a right of reference.
2. Generally filed for newly invented pharmaceuticals. Generally filed for new dosage form, new route of administration, new indication etc. for all already approved pharmaceutical.
Note: 505 (b) (2) application is a type of NDA.

8. Marketing Authorization Application
It is an application filed with the relevant authority in the Europe (Typically the UK’s MHRA or the EMA’s committees for medicinal products for the human use-CHMP) market a drug or medicine as per U.K. MHRA-Application for new active substance are described as ‘full
applications.’ Applications for medicines containing existing active substances are described as ‘abbreviated’ or ‘abridged applications.’

9. An ASMF
An active substance master file is a submission which is made to EMA, MHRA or any other Drug Regulatory Authority in Europe to provide confidential intellectual property or ‘know-how’ of the manufacturer of the active substance. In simple words, ‘it is a submission made to European Drug Regulatory agencies on the confidential information of active substance or active pharmaceutical Ingredient (API).’

i. What are the types of active substances for which ASMFs are submitted?
New active substance existing active substances not included in the European Pharmacopoeia or in the pharmacopoeia of an EU member state.
ASMF is submitted as in two parts
i. Closed part (Restricted).
ii. Open part (Closed part).

10. A CTD
CTD is a [Common Technical Document] which is a set of specifications for application dossier for the registration of medicines and designed to be used across Europe, Japan and in the United States. Quality, Safety and Efficacy information is assembled in a common format through CTD. The CTD is maintained by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for human use. (ICH) CTD format for submission of drug registration applications/dossiers is widely accepted by regulatory authorities of other countries too like Canada, Australia etc.

11. The ICH guideline to be referred for preparation of registration dossier/application of medicines.

i. M4 Guideline
ii. M4Q Guideline
iii. M4S Guideline M4E Guideline

11.1 The modules involved in the CTD are
i. Module 1. Administrative information and prescribing information.
iv. Module 4. Non-Clinical study reports (Toxicology studies).

v. Module 5. Clinical Study Reports (Clinical Studies).

![CTD Modules](image)

**Figure 2: CTD Modules.**

12. **Orange book**

It is the commonly used name for the book “Approved Drugs Products Equivalence Evaluations.” Orange book is published by USFDA. It contains the list of drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug and Cosmetic Act.

13. **Procedures for Approval of API or IP in EU**

i. Centralized Procedure (CP).

ii. Decentralized Procedure (DCP).

iii. Mutual Recognition Procedure (MRP).


14. **CEP-Certificate of Suitability to the monographs of the European Pharmacopoeia**

CEP is the certificate of suitability to the monographs of the European pharmacopoeia or certificate of suitability of monographs of the European Pharmacopoeia or certification of suitability of European Pharmacopoeia monographs. CEP is the certificate which is issued by certification of substance division of European directorate for the quality of medicines (EDQM), when the manufacturer of a substance is suitably controlled by the relevant
monographs of the European Pharmacopoeia.

15. Drug Regulatory Agencies across the world.

1. United States of America—United States Food and Drug Administration (USFDA).
2. United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA).
4. European Union-European Directorate for the Quality of Medicines (EDQM).
5. Australia-Therapeutics Good Administration (TGA).
6. Canada-Therapeutic Products Directorate (TPD) in Health Product and food branch (HPFB) of Health Canada (HC).
7. Japan-Pharmaceutical and Medical Devices Agency (PMDA).
9. Germany-Bundesinstitut für Arzneimittel und Medizinprodukte, (BfArM). Federal Institute for Drugs and Medical Devices.
11. Switzerland-Swiss Agency for Therapeutic Products (SWISSMEDIC).
12. India-Drug Controller General of India (DGCI) who heads Central Drugs Standard Control Organization (CDSCO).
13. Singapore-Health Sciences Authority (HSA).

16. CONCLUSION

Regulatory agencies or regulatory Authorities engages its significant role in the regulatory and control or drug and food products. These agencies also keep control on the standards of manufacturing process relating to cGMP studies of API/IP by providing guidelines, SOP’s and enforcing and enacting various regulator compliances and check before filing a ANDA, IND and NDA to the U.S. FDA, MHRA etc.

Thus regulatory agencies across the world are engaged in activities of continuous monitoring of API/IP and design protocol to study safety of launch of product in market.

Regulatory agencies are also responsible and authorized for withdrawal of marketed product on post marketing surveillance issues.
Regulatory agencies also perform significant roles in combining guidelines across the world and bring them together in the form of Harmonization – ICH guideline.

17. APPENDICES
1. Introduction.
2. Role of a Pharmacy Professional in Regulatory.
2.1 Some of the commonly used Abbreviations in Regulatory procedures are:
4. Technical Terms and Discussion.

Federal and State Regulatory Requirements.
1. Investigational New Drug (IND) application.
3. Abbreviated New Drug Application (ANDA).
4. A DMF-Drug Master File.
5. Type of DMF’s.
6. 505 (b) (2) application.
7. Differences between NDA and 505 (b) (2) application.
9. An ASMF.
10. A CTD.
11. The ICH guideline to be referred for preparation of registration dossier/application of medicines.
11.1 The modules involved in the CTD are:
13. Procedures for Approval of API or IP in EU:
14. CEP-Certificate of Suitability to the monographs of the European Pharmacopoeia.
16. Conclusion.

18. ACKNOWLEDGEMENT
The author would like to express vote of thanks to the ‘World Journal of Pharmaceutical Research’, to recognize the work and publish it in the journal.
19. Conflict of Interest
Author declares no conflict of interest regarding publication.

20. REFERENCES
1. ICH Guideline.