World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Review Article
ISSN: 2583-6579
SJIF Impact Factor: 3.454
Year - 2024
Volume: 3; Issue: 2
Page: 161-183

INSIGHTS OF REGULATORY AFFAIRS IN THE PHARMACEUTICAL INDUSTRY – A REVIEW

Ashok Gorja*, Challa Deepika Reddy, Keerthi Sucharitha and Samperveni Tanmai

Gokaraju Rangaraju College of Pharmacy, Bachupally-500090, Hyderabad, Telangana, India.

Article Received: 01 February 2024 | | ***Article Revised: 22 February 2024*** | | ***Article Accepted: 14 March 2024***

Corresponding Author: Ashok Gorja
Gokaraju Rangaraju College of Pharmacy, Bachupally-500090, Hyderabad, Telangana, India.
DOI: https://doi.org/10.5281/zenodo.10946321

ABSTRACT

Regulatory affairs (RA) plays a vital role in the pharmaceutical industrial department which has the responsibility for obtaining approval for new products arriving in the market and ensuring that approval is maintained for as long as the company wants to keep the product for marketing & it also provides calculated and operational ways and assist for working within regulations to accelerate the development and delivery of safe and effective healthcare products for every particular person all over the world. It behaves as the link between the regulatory authority and the project team and is the passage for communication with the regulatory authority as it moves forward, the target is to ensure that the project plan correctly predicts what the regulatory authority will require before approving the product. The role of regulatory affairs is to develop and carry out a regulatory strategy to make sure that the collective efforts of the drug development team result in a product that is going to be approved by global regulators. Regulatory Affairs has many career choices for graduate students from a scientific background who are interested in communication and teamwork, are complacent with multi-tasking, and have enthusiastic responses to expand their knowledge in the pharmaceutical world. Regulatory Affairs is a gratifying, mentally invigorating, and highly considered profession within the pharmaceutical field.

KEYWORDS: Regulatory authorities, Regulatory agencies, Pharmacy schedule, Pharmacy policy, Worldwide regulatory agencies.

INTRODUCTION

A regulatory affairs professional serves as a liaison between global authorities and the pharmaceutical industry. This profession's mission is to safeguard human health by guaranteeing the efficacy, safety, and quality of medications as well as the appropriateness and accuracy of product information. Internally, it communicates with those involved in clinical research, production, advertising, and marketing, as well as drug improvement. Regulatory Affairs actively participates in post-advertising sports with approved medical products as well as the advancement of modern medicine at every level.[1] A drug regulatory affairs (DRA) expert is crucial to this process at every stage, from planning post-marketing activities to creating successful regulatory strategies after a new molecule is discovered. Regulatory affairs

(RA) specialists assist the organization in avoiding issues brought on by improperly maintained documentation, erroneous scientific conclusions, or subpar data presentation.[2]

Roles and responsibilities[3]

1) Regulatory bodies must examine clinical trials of both newly approved indications for approved medications and non-registered medications.
2) The regulatory bodies are mandated by law to guarantee that the medications that are made available in the nation meet the essential standards for efficacy, quality, and safety.
3) Regulatory authorities have the responsibility to close down an ongoing trial in case there are serious breaches of Good Clinical Practice.
4) Regulatory authorities are responsible for implementing a regulatory system where all clinical trials to be conducted in the country have to register with them.
5) Regulatory bodies will bear the primary duty of encouraging, guaranteeing, and overseeing adherence by authorized ethics committees in a nation to pertinent laws, rules, and regulations, such as the nation's guidelines for good practice in the conduct of clinical trials involving human subjects.
6) Regulatory authorities are responsible for effectively reviewing all the documents (containing both clinical and nonclinical data) before permitting the marketing of a new drug in any country to ensure the efficacy and safety of the drug in humans.
7) Regulatory affairs officers ensure the appropriate licensing, marketing, and legal compliance of a range of pharmaceutical and medical products to control their safety use.
8) RA ensures that a company's goods are compliant with the laws of the areas in which they wish to sell them. Stay current on laws, regulations, and consumer behaviors at the national and international levels. Gather, compile, and assess scientific data from many sources.
9) RA creates and composes concise justifications and arguments for new product licenses and license renewals. Adhere to tight deadlines while preparing submissions for licensing renewals and variations. Track and establish deadlines for approvals for license modifications and renewals.
10) RA body plans and develops product trials and interprets trial data to advise scientists and manufacturers on regulatory requirements to provide strategic advice to senior management throughout the development of a new product.

Amendments

1. Reformulating Drug Products That Contain Carbomers Manufactured With Benzene
2. Direct-to-Consumer Prescription Drug Advertisements
3. Rare Diseases: Considerations for the Development of Drugs and Biological Products
4. Data Standards for Drug and Biological Product Submissions Containing Real-World Data
5. Digital Health Technologies for Remote Data Acquisition in Clinical Investigations
6. Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products
7. Master Protocols for Drug and Biological Product Development
8. Development of Monoclonal Antibody Products Targeting SARS-CoV-2 for Emergency Use Authorization
9. Advanced Manufacturing Technologies Designation Program

10. Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act - Revision 2
11. Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act
12. Translation of Good Laboratory Practice Study Reports: Questions and Answers
13. Submitting Patient-Reported Outcome Data in Cancer Clinical Trials
14. Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessments Using Item Response Theory
15. Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities
16. Policy for Testing of Alcohol (Ethanol) and Isopropyl Alcohol for Methanol
17. Diabetic Foot Infections: Developing Drugs for Treatment
18. Quality Considerations for Topical Ophthalmic Drug Product
19. Stimulant Use Disorders: Developing Drugs for Treatment
20. Weight or Body Surface Area for Ready-to-Use Containers--"Dose Banding" Human Prescription Drug and Biological Products--Labeling for Dosing Based on
21. Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products
22. Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications
23. Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies
24. Regulatory Considerations for Prescription Drug Use-Related Software
25. Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
26. Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act (Revision 1)
27. Labeling for Biosimilar and Interchangeable Biosimilar Products
28. Annual Status Report Information and Other Submissions for Postmarketing Requirements and Commitments
29. Clinical Pharmacology Considerations for Peptide Drug Products
30. Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions for Investigational Drugs and Biological Products

Overview of Drug Regulatory Authority

An independent enforcement organization established by the government to supervise and implement occupational health and safety standards is known as a regulatory authority. Establishing, bolstering, and ensuring constant adherence to safety standards are the responsibilities of the regulatory authority.[3]

The regulatory body's responsibilities include setting requirements, terms, limitations, and guidelines for work-related activities and ensuring that they are followed. While a vast range of professionals are covered by regulatory bodies, not all professions fall under their jurisdiction. Some occupations continue to be self-regulated.

Regulatory agencies work in the fields of secondary legislation, administrative law, regulatory law, and rulemaking, which is the process of codifying and implementing rules and regulations and imposing monitoring or oversight for the

general public's benefit. The difficulties of some regulatory and directing responsibilities as well as the negative effects of political meddling justify the establishment of independent regulatory agencies.

While some independent regulatory bodies conduct audits or investigations, others have the authority to impose fines and mandate specific actions on the pertinent parties. A company or organization frequently needs to apply for a license from the sector regulator to operate in a given industry. This license will specify the rules that businesses or organizations involved in the industry have to follow.

Regulatory Authority of India - CDSCO

The Central Drugs Standard Control Organisation (CDSCO) under the Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India is the National Regulatory Authority (NRA) of India. Its headquarters is located at FDA Bhawan, Kotla Road, New Delhi, and also has nine zonal offices, seven sub-zonal offices, eighteen Port offices, seven central laboratories, and six mini labs spread across the country.[4]

The Drugs & Cosmetics Act, 1940 and rules 1945 have entrusted various responsibilities to central & state regulators for regulation of drugs & cosmetics. It envisages uniform implementation of the provisions of the Act & Rules made there under for ensuring the safety, rights and well-being of the patients by regulating the drugs and cosmetics. CDSCO is constantly thriving upon to bring out transparency, accountability and uniformity in its services in order to ensure safety, efficacy and quality of the medical product manufactured, imported and distributed in the country.

Under the Drugs and Cosmetics Act, CDSCO is responsible for approval of Drugs, Conduct of Clinical Trials, laying down the standards for Drugs, control over the quality of imported Drugs in the country and coordination of the activities of State Drug Control Organizations by providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act. Further CDSCO along with state regulators, is jointly responsible for grant of licenses of certain specialized categories of critical Drugs such as blood and blood products, I. V. Fluids, Vaccine and Sera.

Major functions of CDSCO

Regulatory control over the import of drugs, approval of new drugs and clinical trials, meetings of Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB), approval of certain licenses as Central License Approving Authority is exercised by the CDSCO headquarters.[5]

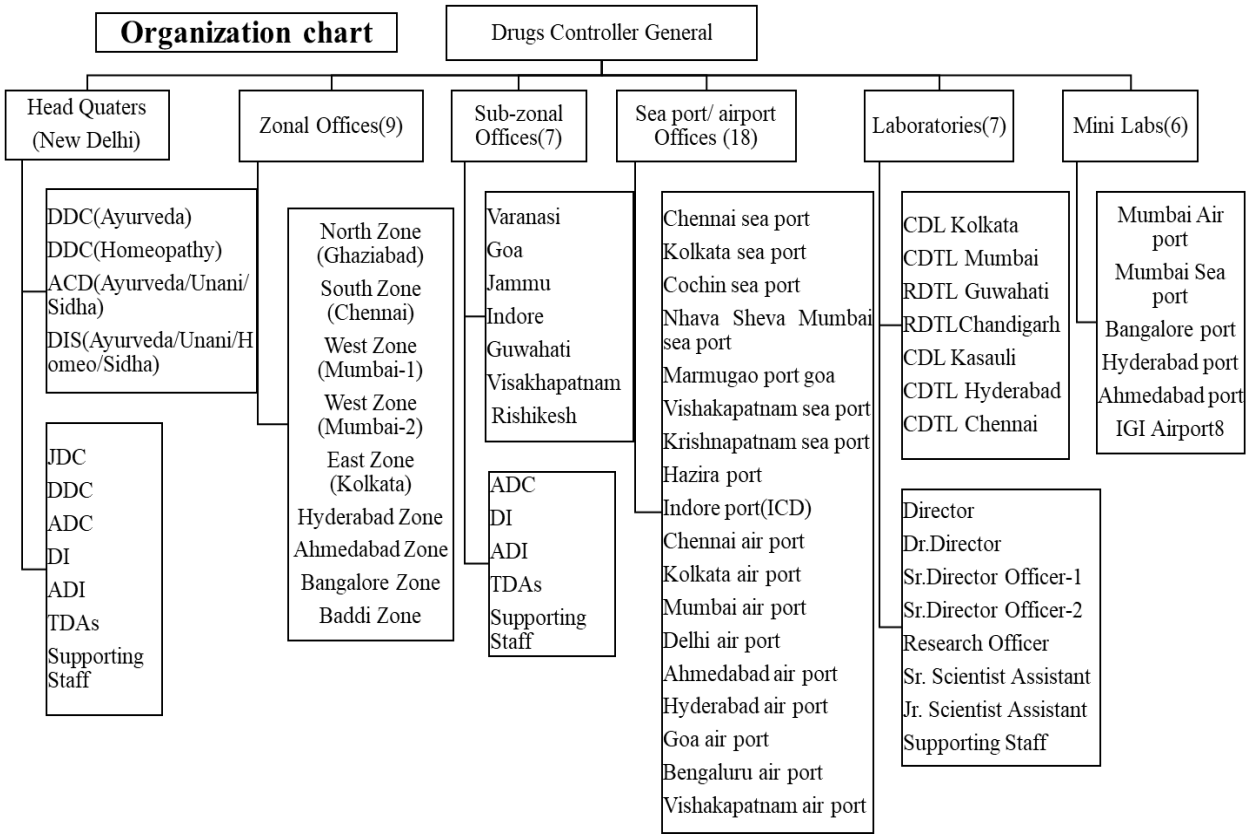

Figure 1: Organization chart of CDSCO.

Regulatory Authority of Europe - European Medicine Agency (EMA)[6]

The European Medicines Agency (EMA) protects and promotes human and animal health by evaluating and monitoring medicines within the European Union (EU) and the European Economic Area (EEA). It fosters research into novel medications and encourages development through its scientific guidelines, scientific advising program, and incentives, thereby transforming medical science advancement into medicines that have genuine health benefits for people. Specifically, it encourages the creation of pediatric medications and pharmaceuticals to treat uncommon illnesses.

EMA's scientific committees provide independent recommendations on medicines for human and veterinary use, based on a comprehensive scientific evaluation of data. The Agency's evaluations of marketing-authorization applications submitted through the centralized procedure provide the basis for the authorization of medicines in Europe. They also underpin important decisions about medicines marketed in Europe, referred to EMA through referral procedures. EMA coordinates inspections in connection with the assessment of marketing authorization applications or matters referred to its committees. EMA is committed to enabling timely patient access to new medicines and plays a vital role in supporting medicine development for the benefit of patients.

The Agency fulfils its responsibilities by:

- Facilitating the development of medicines & access to them
- Evaluating applications for marketing authorizations
- Monitoring the safety of medicines throughout their lifecycle
- Providing information to healthcare professionals & patients

- Developing guidelines and setting standards;
- Coordinating the monitoring of pharmaceutical companies' compliance with their pharmacovigilance obligations;
- Contributing to international pharmacovigilance activities with authorities outside the EU;
- Informing the public on the safety of medicines and cooperating with external parties, in particular representatives of patients and healthcare professionals.

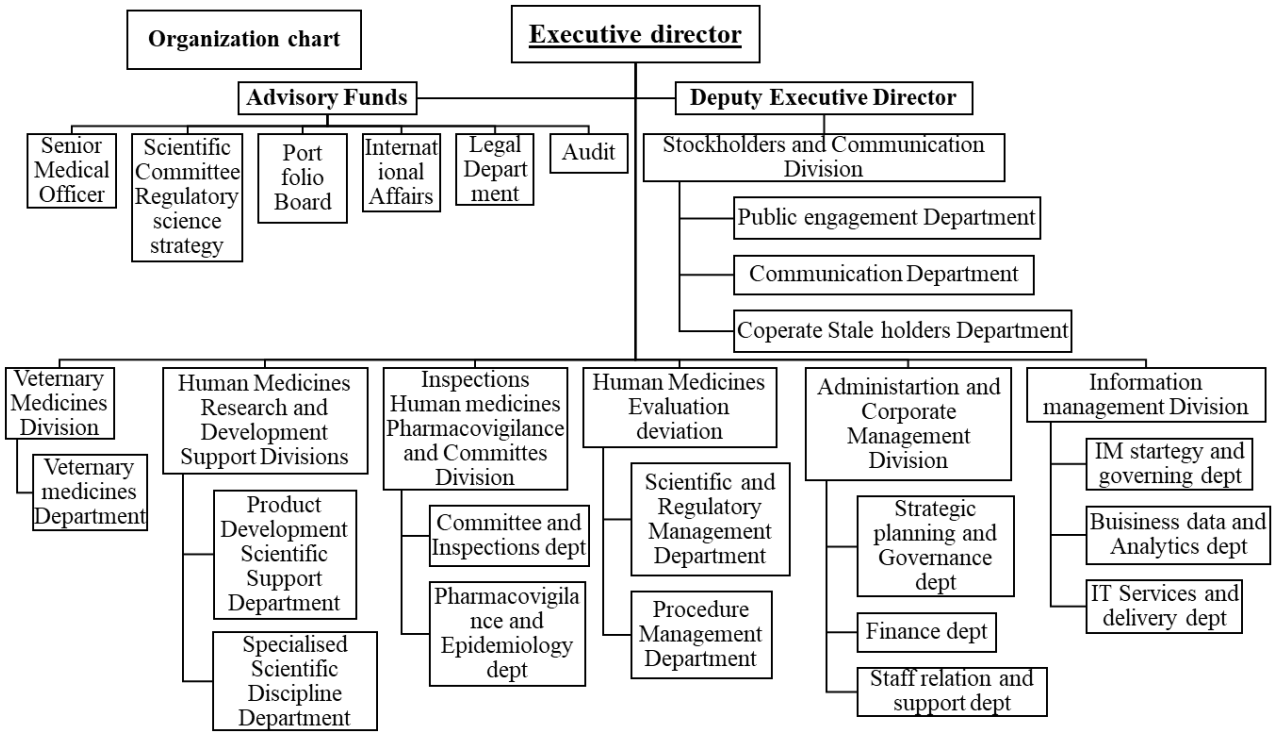

Figure 2: Organization chart of European Medicines Agency.

Regulatory Authority of Australia -Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, and blood and blood products. Almost any product for which therapeutic claims are made must be entered in the Australian Register of Therapeutic Goods (ARTG) before it can be supplied in Australia.[7]

When new safety information for medicines is identified, the Therapeutic Goods Administration (TGA) works with the sponsors to update Product Information (PI) to ensure that health professionals and consumers have access to this information. New safety information can be identified through the TGA's ongoing safety monitoring activities or uncovered and submitted by sponsors themselves. Please see below details of some medicines that have recently had safety-related updates to their PI.

The TGA regulates the supply of:

- Medicines prescribed by a doctor or dentist
- Medicines available from behind the pharmacy counter
- Medicines available in the general pharmacy
- Medicines available from supermarkets

- Complementary medicines, these include vitamins, herbal and traditional medicines
- Medical devices, from simple devices like bandages to complex technologies like heart pacemakers
- Products used to test for various diseases or conditions (in vitro diagnostic devices), such as blood tests; and
- Vaccines, blood products, and other biologics and the manufacturing and advertising of these products.

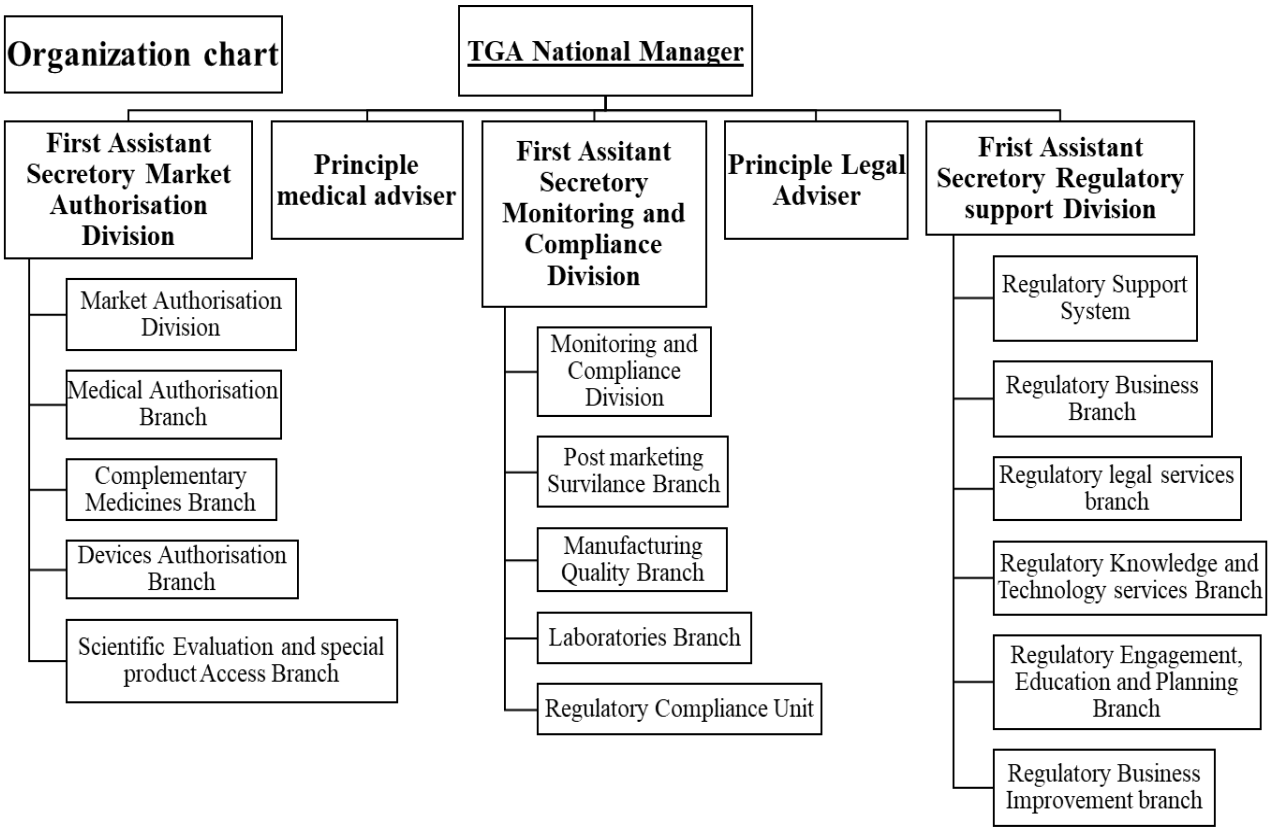

Figure 3: Organization chart of TGA.

Regulatory Authority of Japan - Pharmaceutical and Medical Device Agency (PMDA)

A Japanese regulatory body called PMDA (Pharmaceuticals and Medical Devices Agency) collaborates with the Ministry of Health, Labour, and Welfare. Maintaining the quality, safety, and efficacy of medications and medical equipment is our responsibility to safeguard the public's health. To monitor the safety of pharmaceuticals and medical devices once they are marketed, we do scientific evaluations of their marketing permission applications. Compensation for relief from adverse medication reactions and infections caused by pharmaceuticals or biological products falls under our purview as well.[8]

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission by the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.

- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- We play an active role within the international community by promoting international harmonization.
- We conduct services in a way that is trusted by the public based on our experiences from the past.

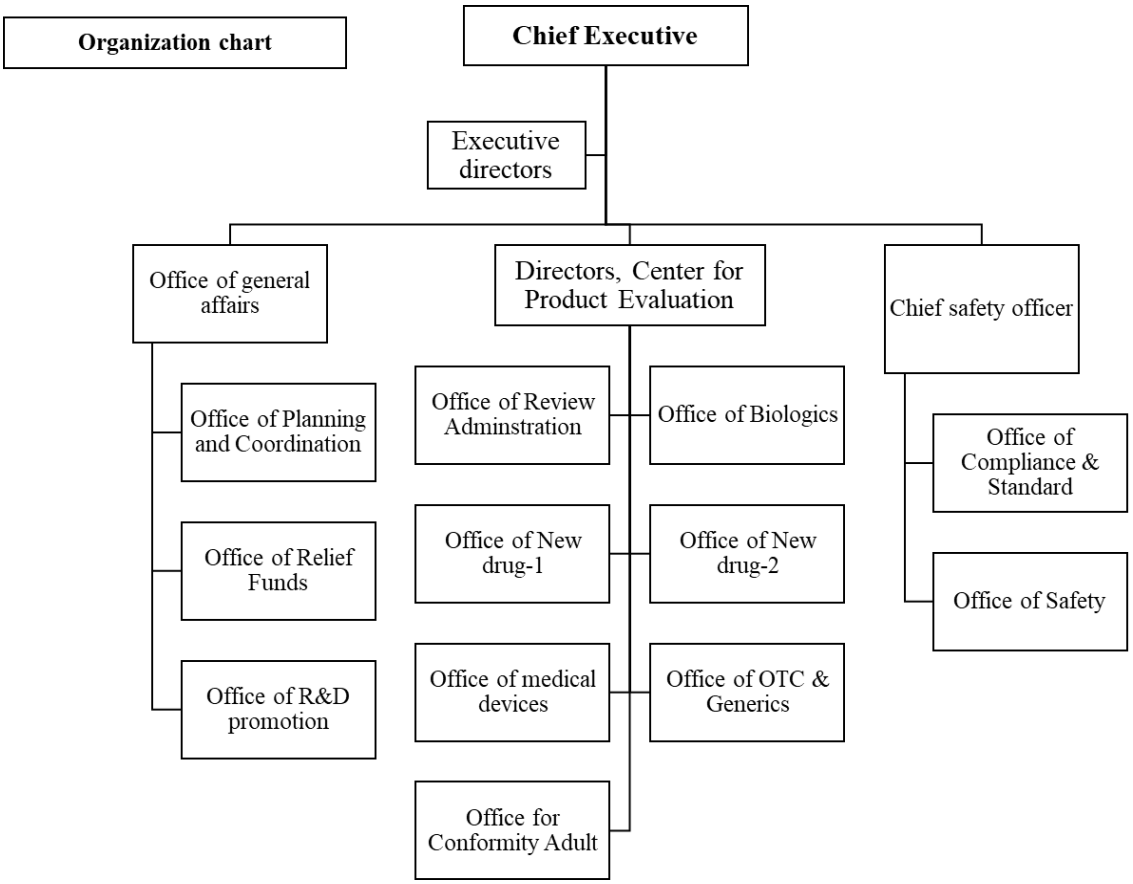

Figure 4: Organization chart of PMDA.

Regulatory Authority of United States - Food and Drug Administration (FDA)

The federal organisation in charge of examining, authorising, and regulating medical products, including prescription medications and medical devices, is the United States Food and Drug Administration (FDA). In addition, it controls a wide range of other goods, including as tobacco, biological products, food, cosmetics, veterinary medications, and items that produce radiation. The Pure Food and Drugs Act of 1906, a statute designed to prevent manufacturing abuses in the consumer product market, marked the beginning of the agency. In 1930, the Food and Drug Administration was given its formal name. Among the FDA's regulatory duties are collaborating with manufacturers to recall defective products and gathering information on adverse events, or harm or side effects brought on by medications, medical equipment, and vaccinations. The FDA may receive reports of adverse events from manufacturers, physicians, and patients.[9]

The original goal of the US Food and Drug Administration was to control the sale of medications and food products with false labels. In addition to regulating pharmaceuticals, the agency's purview has expanded over time to encompass the approval and oversight of medical devices. It also oversees vaccine, medication, and equipment recalls. When necessary, the organisation gathers reports of unfavourable incidents and alerts the public.

The FDA's Regulatory Responsibilities are:

- Protecting the public health by ensuring the safety, effectiveness and security of human and veterinary drugs, medical devices, vaccines and biological products
- Providing the public with accurate, science-based information to ensure the safe and appropriate use of medical products and foods
- Ensuring the safety and proper labeling of food
- Regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors
- Protecting the public from radiation released by certain electronic products
- The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.
- FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.
- FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.
- FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.
- Scientifically trained staff must supervise production of these medicines
- Licensing of facilities by PHS
- Inspections of establishments and testing of biologics for purity and potency
- Standards issued for products
- Enhanced scientific legitimacy on firms and their products
- Scientific infrastructure mandated under the law helped promote new product development.

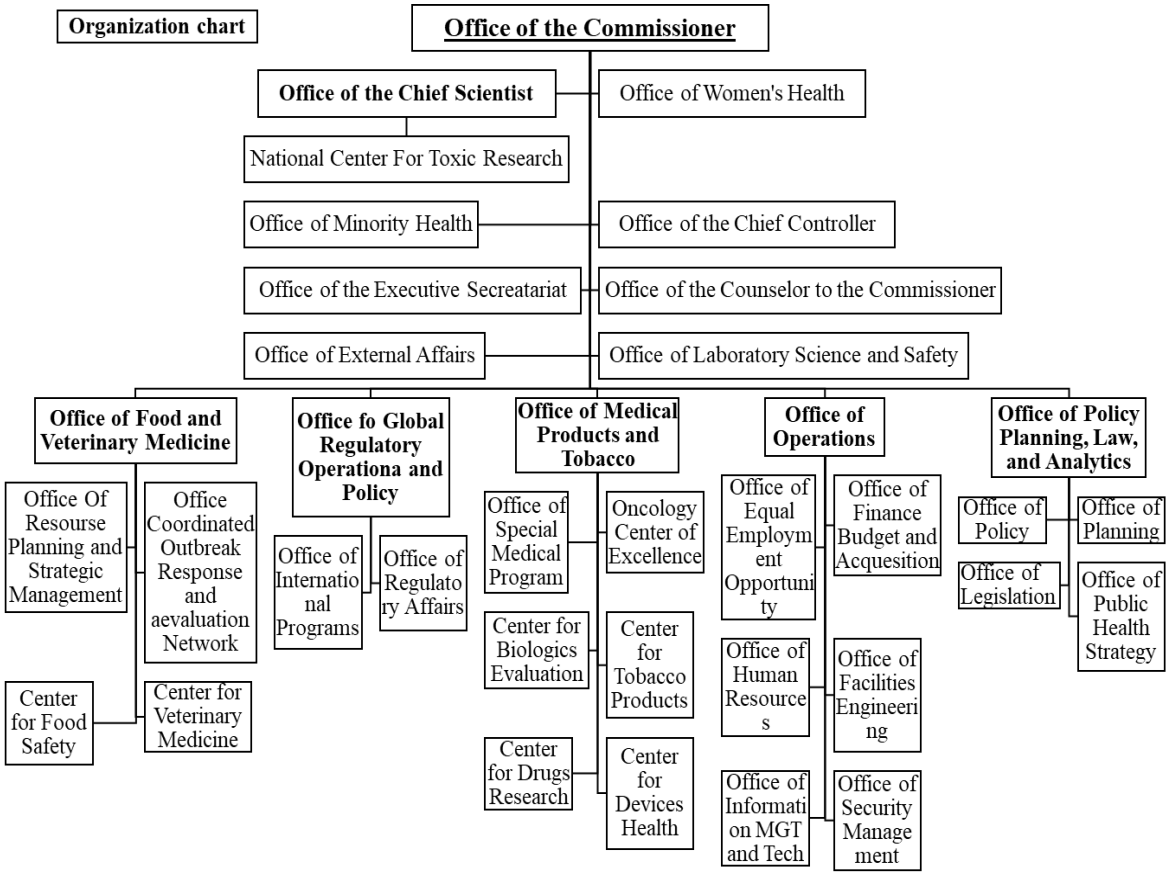

Figure 5: Organization chart of FDA.[10]

Regulatory Authority of Canada - Health Canada[11]

Foods, pharmaceuticals, medical equipment, biologics (including items used in cellular treatment), natural health products, and other health products are all under the purview of Health Canada. Part C of the Food and Drug Regulations contains regulations particular to cellular treatment, while the Food and Drugs Act of 1920, as modified, grants Health Canada overall regulatory power.

Roles and Responsibilities

- Conclude multi-year health accord agreements with provinces and territories with a focus on improving home care and mental health services, as well as joint federal-provincial-territorial actions to lower the cost of prescription drugs and support more innovative models of care.
- Address outstanding and emerging Canada Health Act issues through consistent interpretation and even-handed enforcement actions across Canada.

  • Implement Health Canada's Regulatory Transparency and Openness Framework and Action Plan by informing and engaging Canadians on important health and safety issues, and by supporting consumer confidence through the provision of more information so that Canadians can see how the Department enables industry compliance and enforces regulatory rules. The Department will continue to work with industry to promote compliance and adopt strong safety standards.
- Implement the Healthy Eating Strategy as part of the Government of Canada's vision for a Healthy Canada. Under the Strategy, the Department will provide Canadians with tools such as modernized food labels to support them in

making better informed food choices, create conditions for healthier food options that are lower in sodium and trans fats, and restrict marketing of unhealthy foods to children and revise Canada's Food Guide.

- Work with the Departments of Justice and Public Safety and Emergency Preparedness towards the legalization and strict regulation of cannabis to keep it out of the hands of youth and to keep profits out of the hands of criminals.

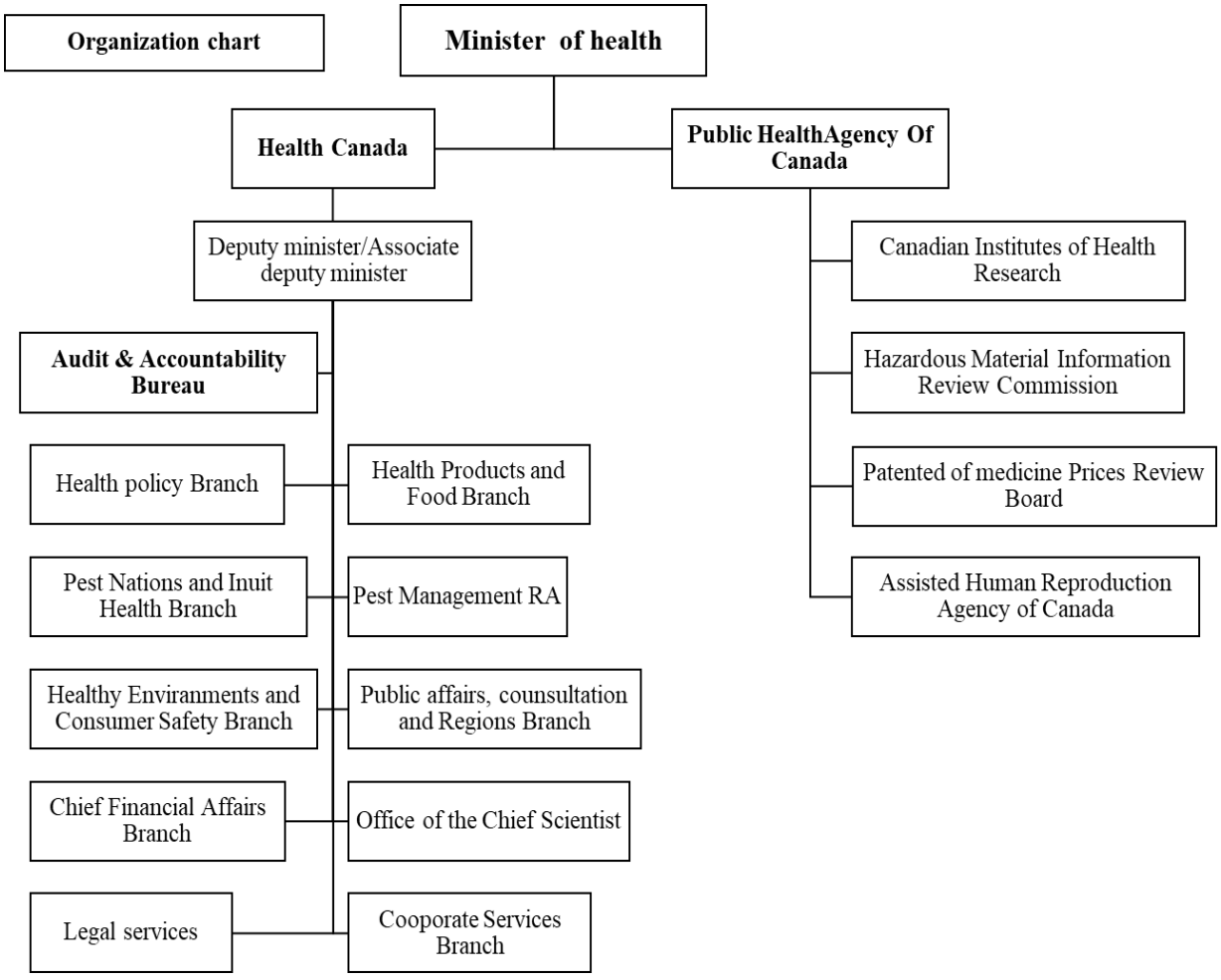

Figure 6: Organization chart of Health Canada.

CTD and eCTD

Common Technical Document (CTD)

The Common Technical Document (CTD)[13] was created to give technical documentation submitted with an application for the registration of a pharmaceutical product for human use a standard format across Europe, the United States, and Japan.

There are five primary modules in the CTD dossier:

- Prescription and administrative information is covered in Module 1

Module 1 is not strictly included in the CTD since it contains documents that are specific to each region, e.g. application forms or the proposed label. This module will not be discussed in any further detail in this article since the content and format of this module is specific to individual Regulatory Authorities.

- Overviews and summaries of Modules 3–5 are covered in Module 2

Module 2 contains seven sections that should be maintained in the following order:

2.1 Table of contents

2.2 Introduction

2.3 Quality Overall Summary

2.4 Non-clinical Overview

2.5 Clinical Overview

2.6 Non-clinical Written and Tabulated Summaries

2.7 Clinical Summary.

- Pharmaceutical documentation quality is covered in Module 3

Module 3 presents the chemistry, manufacturing, and controls reports for the product included in the registration dossier. Full details of what should be included in Module 3 are provided in the ICH M4Q guideline. 5 Sections on both drug substance and drug product are included in this module. The main headings in this section (that must not be altered) are as follows:

3.1 Table of contents

3.2 Body of data

3.2. S Drug Substance

3.2. P+ Drug Product

3.3 Literature references used in Module 3

- Non-clinical reports (pharmacology/toxicology) are covered in Module 4

Module 4 presents the non-clinical reports included in the dossier. The structure and content of Module 4 is specified in the ICH M4S guidelines.7 The main headings in this section (that must not be altered) are as follows:

4.1 Table of contents

4.2 Study reports

4.2.1 Pharmacology

4.2.2 Pharmacokinetics

4.2.3 Toxicology

4.3 Literature references used in Module 4.

- Clinical study reports (clinical trials) are covered in Module 5.

Module 5 presents the clinical reports included in the dossier. The structure and content of Module 5 is specified in the ICH M4E guidelines, 9 which provided a specific placement of clinical study reports and related information to simplify preparation and review and to ensure completeness. The placement of a report is determined by the primary objective of the study, with each report appearing in only one section. If there are multiple objectives, the study should be cross-referenced in the various sections. The main headings in this section (that must not be altered) are as follows:

5.1 Table of contents

5.2 Tabular listing of all clinical studies

5.3 Clinical study reports

5.3.1 Reports of biopharmaceutic studies

5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials
5.3.3 Reports of human pharmacokinetic (PK) studies
5.3.4 Reports of human pharmacodynamic (PD) studies
5.3.5 Reports of efficacy and safety studies
5.3.6 Reports of post-marketing experience
5.3.7 Case report forms and individual patient listings
5.4 Literature references.

Each module's content is described in detail in the guidelines, and most submissions now need to use the CTD format for submission dossiers. While most areas have successfully developed the CTD and all dossiers now utilise the CTD format (newer dossiers are migrating to the eCTD format), others continue to maintain elements of their pre-CTD dossier requirements. The FDA's requirement to submit an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS) in the USA submission is the most common example of this, even though the intention was for the Clinical Summary to take their place (Module 2.7.3 Summary of Clinical Efficacy replaced the ISE, and Module 2.7.4 Summary of Clinical Safety replaced the ISS). Therefore, the advice given is to include the entire ISE and ISS in Module 5 and then condense this information into a format suitable for summaries in the Module 2.7 publications.

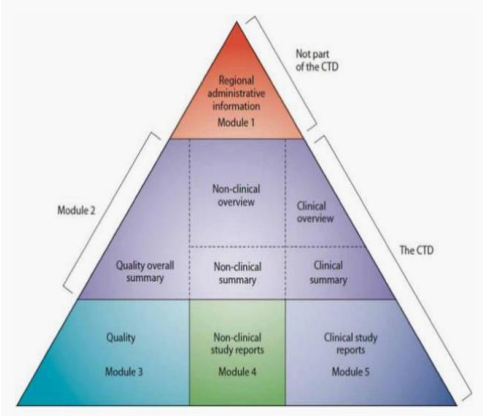

Figure 7: CTD Triangle.

Electronic Common Technical Document (eCTD)

Electronic Common Technical Document (eCTD) is a topic of increasing interest in the pharmaceutical environment.[14] Electronic Common Technical Document (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory information. Since June 2003, applicants have had the option of submitting an eCTD in parallel with the paper submission (Common Technical Document), following sign-off by the International Conference on Harmonisation Steering Committee of the eCTD Specification document at Step 4. It is designed to make regulatory submissions easier and more efficient for drug makers and for regulators.[15] When it comes to eCTD submission, there continues to be differences among different countries and even ICH regions. The standardization that electronic submissions will bring will allow for much greater consistency not only for the regulators but also for organizations. It is important that eCTD ready documents are prepared by authoring them in eCTD compliant templates. If this is not undertaken, a large amount of the “publishing time” is spent in document reformatting. As the move from paper-based to eCTD submissions continues around the world, a multitude of challenges are to be faced regulatory departments.

This paper describes eCTD History, Benefits of Implementing, Challenges, Modules, Risks involved in eCTD publishing and Quality Control.[16]

Regulatory Approval Process

The regulatory approval process stands as a pivotal gateway in the development and commercialization of pharmaceuticals, medical devices, biologics, and other healthcare products. Governed by stringent regulations and overseen by regulatory agencies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and similar bodies worldwide, this process ensures that products reaching the market meet rigorous standards of safety, efficacy, and quality. Understanding the fundamentals of the regulatory approval process is imperative for stakeholders across the healthcare industry, encompassing pharmaceutical companies, medical device manufacturers, regulatory affairs professionals, clinicians, and patients. This essay aims to provide a comprehensive overview of the regulatory approval process, delineating its key stages, underlying principles, and the roles played by various stakeholders.[17]

Approval and Timelines Involved in IND

IND Submission

The submission of an IND application[18] marks the formal initiation of the regulatory review process for a new investigational drug. Sponsors compile a comprehensive dossier of information about the investigational drug, incorporating details regarding its chemical structure, manufacturing procedures, preclinical pharmacology and toxicology findings, and proposed protocols for clinical trials. This dossier is electronically submitted to the FDA via the Electronic Submission Gateway (ESG) in adherence to specified formats and standards.

30-Day Review Period

Following the receipt of an IND application, the FDA embarks on an initial review process aimed at evaluating the safety aspects associated with initiating clinical trials involving the investigational drug. Typically spanning 30 days, this review involves an assessment of the submitted data to ensure that prospective human participants in the proposed clinical trials are not exposed to undue risks. Should the FDA identify any concerns or queries during this review period, it reserves the right to issue a clinical hold, thereby temporarily suspending the initiation of clinical trials until the identified issues are satisfactorily addressed.

Clinical Trials

Assuming no significant concerns or clinical holds are issued by the FDA, sponsors proceed with the implementation of clinical trials delineated in the IND application. These trials progress through three distinct phases:

Phase 1: Conducted primarily to evaluate the safety profile and determine appropriate dosing of the investigational drug, typically involving a small cohort of healthy volunteers or patients.

Phase 2: Focused on assessing both efficacy and further safety parameters in a larger patient population afflicted with the targeted disease or condition, thereby providing insights into the drug's effectiveness and safety profile in a more diverse demographic.

Phase 3: Encompassing large-scale studies conducted across multiple sites and involving a broad patient population, aimed at confirming the drug's efficacy, further delineating its safety profile, and gathering additional data pertaining to its benefits and risks.

Ongoing Communication with FDA

Throughout the continuum of clinical trial activities, sponsors maintain an open channel of communication with the FDA. Regular updates concerning trial progress, safety data, and any significant findings that may impact the safety or efficacy of the investigational drug are provided to the regulatory agency. This ongoing communication framework ensures that the FDA remains apprised of developments and can furnish timely feedback or guidance as necessitated by evolving circumstances.

New Drug Application (NDA) Submission

Should the results emanating from clinical trials prove positive and substantiate the efficacy and safety of the investigational drug, sponsors may elect to compile and submit a New Drug Application (NDA) to the FDA. The NDA encompasses a comprehensive compilation of data derived from all preclinical and clinical studies conducted on the drug, along with detailed proposals pertaining to labeling and manufacturing specifications.[19]

FDA Review of NDA

The FDA undertakes an exhaustive review of the NDA, meticulously scrutinizing all submitted data to evaluate the drug's safety, efficacy, and quality. This multifaceted review process encompasses a comprehensive assessment conducted by various specialized disciplines within the FDA, including pharmacology, toxicology, clinical research, and manufacturing. The overarching objective of this review is to ascertain whether the drug's therapeutic benefits outweigh its associated risks and whether it fulfills the requisite criteria for regulatory approval.

FDA Approval

Upon completion of the review process and subsequent evaluation of the NDA, if the FDA deems the investigational drug to be safe and effective for its intended use, it grants approval for the NDA, thereby conferring marketing authorization for the drug. With FDA approval secured, sponsors are authorized to commence marketing activities for the drug, specifically targeting the indications delineated within the approved labeling.

Timeline

The timeline for the entirety of the IND approval process, inclusive of subsequent stages, is inherently variable and contingent upon a myriad of factors. These factors encompass the intrinsic complexity of the drug under evaluation, the comprehensiveness and quality of available data, the responsiveness of regulatory authorities such as the FDA, and the emergence of unforeseen contingencies during the clinical trial phase. In general, the progression from IND submission to FDA approval encompasses a protracted timeline spanning several years, often ranging from 5 to 10 years or more, particularly in scenarios involving novel drugs characterized by intricate mechanisms of action or targeting diseases for which therapeutic options are limited. It is imperative to note, however, that expedited pathways may be accessible for select drugs aimed at addressing severe or life-threatening conditions, potentially culminating in a more abbreviated timeline for regulatory approval.

National Drug Application

When a company wants to market a new drug in the US, it must submit a marketing application to the FDA for review and approval.

An NDA is a submitted request for permission to market a new drug product, including new molecular entities (NMEs), small molecules, biologics, vaccines, new combinations, new indications, and more.

The NDA must be submitted in a standard format, which is organized using the Common Technical Document format, a technical standard for all agency submissions starting from the IND phase. This format provides a standardized way of organizing and submitting regulatory information, and it helps to ensure that the information is consistent and easily accessible.

It's typical for sponsors to use the electronic common technical document (eCTD) format, as it is regarded as the fastest delivery method to move the NDA process along between the sponsor and FDA.

Over the years, the application process has evolved to include more stringent requirements and greater scrutiny of the data submitted by drug manufacturers due to advancements in scientific understanding of drugs and their effects as well as increased public attention to drug safety and efficacy.

Components of the NDA

1. Preclinical Data

This section includes results from laboratory studies and animal testing conducted to assess the pharmacological activity, pharmacokinetics, and toxicology of the drug. These data provide insights into the potential risks and benefits of the drug before human trials begin.

2. Clinical Trial Data

Clinical trial data are collected from human studies conducted in multiple phases. Phase 1 trials typically focus on safety and dosage, Phase 2 trials assess efficacy and further safety, and Phase 3 trials confirm efficacy and monitor adverse reactions in larger patient populations. These data are crucial in demonstrating the drug's safety and efficacy in treating the targeted disease or condition.

3. Chemistry, Manufacturing, and Controls (CMC) Information

This section provides detailed information about the drug's chemical composition, manufacturing process, and quality control measures. It ensures that the drug product is consistently produced to meet quality standards and specifications.

4. Proposed Labeling

Proposed labeling includes essential information about the drug product, such as prescribing information, dosage and administration instructions, contraindications, warnings, precautions, and adverse reactions. This information helps healthcare providers and patients use the drug safely and effectively.

5. Regulatory Overview

This section summarizes the regulatory history of the drug, including previous interactions with regulatory agencies and the status of prior regulatory submissions. It provides context for the NDA submission and helps regulatory authorities understand the drug's development pathway.

6. Patent Information

Patent information outlines any patents or exclusivity rights associated with the drug product or its components. It is essential for understanding the drug's intellectual property landscape and may impact market exclusivity and commercialization strategies.

NDA Review Process

1. Validation

Upon receipt of the NDA, the regulatory agency conducts an initial review to ensure that the submission is complete and meets the requirements for validation. This includes verifying that all required documentation and data are included.

2. Filing Review

The filing review stage involves a preliminary assessment of the NDA to determine whether it meets the regulatory criteria for acceptance and filing. This includes evaluating the completeness of the submission and confirming that the data supports the proposed indications for use.

3. Substantive Review

During the substantive review, regulatory reviewers examine the submitted data in detail to assess the drug's safety, efficacy, and quality. They may request additional information or clarification from the sponsor and conduct thorough analyses to ensure that the drug meets regulatory standards.

Abbreviated New Drug Application (ANDA)

Abbreviated New Drug Application is a regulatory submission to the US Food and Drug Administration (FDA) for generic drugs. An ANDA must provide information that demonstrates a proposed generic drug is the same as an already approved reference listed drug (RLD) in terms of safety, efficacy, and quality.

This information includes details about the active ingredients, conditions of use, method of administration, form (e.g. tablet, capsule), potency, and labeling of the drug, as well as evidence of the drug’s bioavailability, which is a crucial factor in demonstrating bioequivalence between a generic drug and its reference listed drug. The FDA requires that generic drugs have comparable bioavailability to the RLD to be approved and sold in the market.[19]

However, the application may include certain differences from an RLD, such as changes granted through a suitability petition or other acceptable variations, as long as clinical trials are not required to demonstrate the safety or efficacy of the drug product being proposed in the ANDA. Differences include things like inactive components, labeling, or container closure systems.

It is important to note that an ANDA cannot be submitted if clinical trials are necessary to establish the safety and effectiveness of the proposed drug product. In such cases, the drug product must undergo additional testing and evaluation before an ANDA can be submitted to the FDA.

Historically, the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, established the ANDA process to streamline the approval of generic drugs, adding sections 505(b)(2) and 505(j) to the Federal Food, Drug, and Cosmetic Act, or FD&C Act.

The act aimed to increase competition and reduce the cost of prescription drugs by allowing generic drug manufacturers to skip some of the more expensive clinical trials required for new medicines as long as the generic drug is considered equivalent to an already approved drug.

This has increased the availability of lower-cost generic drugs, which has played a significant role in making prescription drugs more affordable for millions of people, and reflects Congress's efforts to strike a balance between expanding access to generic drugs and providing new incentives for drug development through exclusivities and patent term extensions.

As a result, the FD&C Act now outlines two distinct pathways for drug approval: New Drug Applications (NDAs) and Abbreviated New Drug Applications.

ANDAs can be divided into two categories

1. ANDA Application: This application is submitted and approved under section 505(j) of the FD&C Act for a drug identical to a previously approved drug. The ANDA relies on the FDA's previous determination that the reference listed drug (RLD) is safe and effective.
2. Petitioned ANDA: This type of ANDA is for a drug that differs from the RLD in terms of its dosage form, route of administration, strength, or active ingredient. In this case, the FDA has determined, in response to a petition submitted under section 505(j)(2)(C) of the FD&C Act, that additional studies are not necessary to establish the safety and effectiveness of the proposed drug. A petitioned ANDA is expected to have the same therapeutic effect as the reference listed drug.

How Do You Submit an ANDA?

The steps involved in submitting an Abbreviated New Drug Application (ANDA) for FDA approval include the following:

1. **Pre-ANDA Preparation:** In this step, the sponsor should gather information on the reference listed drug, including its chemical and pharmacological properties, formulation, labeling, and regulatory history. This information determines if the generic drug is the same as the reference-listed drug.
2. **Preparation of the ANDA:** The sponsor then prepares the ANDA, which includes data on the chemical, pharmacological, and clinical properties of the generic drug. This information demonstrates the generic drug's similar to the reference listed drug. The ANDA also includes information on the manufacturing process, quality control, and proposed labeling.
3. **Submission of the ANDA:** Once the ANDA is complete, the sponsor submits it to the FDA's Center for Drug Evaluation and Research (CDER). You must submit the ANDA electronically through the FDA's electronic submissions gateway.
4. **FDA Review:** The FDA reviews the ANDA to determine if it meets the regulatory requirements for approval. The review process typically takes around 30 months, although the FDA can expedite the review of drugs that treat severe conditions or address unmet medical needs.
5. **FDA Decision:** Once the review is complete, the FDA either approves or denies the ANDA. If approved, the sponsor can start selling the generic drug. The time required for each step of the ANDA process can vary depending on the complexity of the drug and the availability of information. Pre-ANDA and ANDA preparation

can take several months to a year, while the FDA review process typically takes around 30 months. Furthermore, the time between submission and decision can vary depending on the type of drug and the FDA's workload.

How to Determine Whether to Submit an ANDA or 505(b)(2) Application

The decision to submit an ANDA or a 505(b)(2) application depends on several factors, including the type of product under development (its specific characteristics) and the availability of existing information about the product.

As stated, a sponsor submits an ANDA to the FDA for evaluation, which leads to the approval or rejection of a generic drug that is similar to a brand-name drug that has been approved already. The approval is based on the safety and efficacy data of the previously approved drug, only requiring supplementary data to prove its equivalence to the benchmark product.

On the other hand, a 505(b)(2) application is used for the approval of new drug products that are not identical to a previously approved drug but rely on information from a previously approved drug for some, but not all, of the required safety and efficacy data. A 505(b)(2) application may be appropriate for developing new drug products with a different formulation, dosing regimen, or route of administration than an already approved drug.

A thorough evaluation of the drug product and its development history is necessary to determine the appropriate regulatory pathway.

Introduction to General Regulatory Concepts

Orange Book / Approved Drug Products with Therapeutic Equivalence Evaluation

Approved Drug Products with Therapeutic Equivalence Evaluations (the List, also known as the Orange Book) is a publication that identifies drug products that have been approved by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act.[20]

Salient Points

The FDA maintains the Orange Book, a publicly available list that lists all pharmacological products that are both safe and effective. The list is updated only with medications that have completed phase 3 clinical trials with success.

The Orange Book helps locate generic drug substitutes, which frequently come at a significantly reduced cost to patient.

Contents of Orange Book

It is composed of four parts:

- Approved prescription drugs with therapeutic equivalence assessments.
- Approved over-the-counter (OTC) drug goods for those pharmaceuticals that can't be marketed without NDAs or ANDAs because they are not subject to 505G.
- Drug products with approval under Section 505 of the FD&C Act administered by the Center for Biologics Evaluation and Research.
- A cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined that they were withdrawn from sale for safety

or effectiveness reasons, or have had their approvals withdrawn for other than safety or effectiveness reasons after being discontinued from marketing.

Purple Book

Purple Book is a searchable online database that contains information about biological products, including biosimilar and interchangeable biological products, licensed (approved) by the FDA under the Public Health Service (PHS) Act.

Currently, the searchable database contains information about all FDA-licensed biological products regulated by CDER, including licensed biosimilar and interchangeable products, and their reference products, and FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by CBER.

Salient Points

It includes the date a biological product was licensed under 351(a) of the PHS Act and whether FDA evaluated the biological product for reference product exclusivity under section 351(k)(7) of the PHS Act.

It also includes whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference biological product.

Code of Federal Regulations

The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the *Federal Register* by the executive departments and agencies of the Federal Government.

It is divided into 50 titles that represent broad areas subject to Federal regulation. Each volume of the CFR is updated once each calendar year and is issued every quarter. The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the *Federal Register* by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation. Each volume of the CFR is updated once each calendar year and is issued every quarter. The 50 subject matter titles contain one or more individual volumes, which are updated once each calendar year, on a staggered basis.

The annual update cycle is as follows:

- Titles 1-16 are revised as of January 1
- Titles 17-27 are revised as of April 1
- Titles 28-41 are revised as of July 1
- Titles 42-50 are revised as of October 1

Organisation of CFR

The CFR is divided into 50 titles that represent broad areas subject to Federal regulation. Each title is divided into chapters, which usually bear the name of the issuing agency. Each chapter is further subdivided into parts that cover specific regulatory areas. Large parts may be subdivided into subparts. All parts are organized in sections, and most citations to the CFR refer to material at the section level.[20]

Structure of CFR Citation

Title: The numeric value to the left of "CFR"

Part: The numeric value to the right of "CFR" and preceding the period (".")

Section/Subpart: The numeric value to the right of the period (".") A subpart is a letter of the alphabet (A-Z) that is used to retrieve an entire subpart of the CFR rather than many individual sections.

Revision Year: Four digit year from the "Revised as of" text represents the year being cited. The revision year is not always available when the CFR is cited.

Drug Master File (DMF)

A Drug Master File (DMF) 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 human drugs.

The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder.

The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these.

A DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application.

Types of Drug Master Files

There are five types of DMF's:

Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel

Type II Drug Substance, 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

CONCLUSION

DRA is a rewarding and approachable field that include legal and scientific both dynamic aspects of new drug development. Regulatory governing bodies have been formed all around the world to ensure that medicines for human use satisfy global standards of quality, effectiveness, and safety. For example, FDA, TGA, CDSCO, EMEA, and others. It includes legislation that requires drugs to be trailed, manufactured, tested, and developed according to guidelines given by authority so that they are safe and patients will be well healthy and protected.

REFERENCES

1. Huma, T. and Peng, Z., Introduction to cdcAffairs and Different Regulatory Bodies for Pharmaceutical Products and Impact of Digitalization on Regulatory Affairs. Pharmacology & Pharmacy, 2023; 14: 463-477.
2. Claro, R.A., Spillman, D., Hotaki, L.T., Shum, M., Mouawad, L.S., Santos, G.M., et al., Project Orbis: Global Collaborative Review Program. Clinical Cancer Research, 2020; 26: 6412-6416. https://doi.org/10.1158/1078-0432.CCR-20-3292.
3. Government and Regulatory Bodies around the World. https://Pharmweb.net/pwmirror/pwk/pharmwebk.html
4. Central Drugs Standard Control Organization. [Last accessed on 2023 Dec 20]. Available from: https://www.cdscoonline.gov.in/CDSCO/homepage.
5. Central Drugs Standard Control Organization. [Last accessed on 2017 Feb 20]. Available from: http://www.cdsco.nic.in/html/GCP1.html
6. "European Medicines Agency (EMA) | European Union". europa.eu. 26 February 2020.
7. Australian Government, Department of Health and Aged Care (2021) Australia Canada-Singapore-Switzerland-United Kingdom (Access) Consortium.
8. Nagasaka, Satoru. "An Overview of Pharmaceutical and Medical Device Regulation in Japan" (PDF). Morgan, Lewis & Bockius LLP. Archived from the original (PDF) on 11 February 2014. Retrieved 30 September 2012.
9. *"FDA Overview" (PDF).* Food and Drug Administration. *Archived (PDF)* from the original on November 1, 2013. *Retrieved August 30, 2012*
10. "About the FDA Organization Charts". Food and Drug Administration. August 29, 2014. Archived from the original on July 22, 2015. Retrieved July 19, 2015. FDA is an agency within the Department of Health and Human Services and consists of nine Centers and Offices, which are listed on the menu to the left.
11. "Health Portfolio". Canada.ca. Government of Canada (2017). Retrieved 29 April 2020.
12. Socal, M., Sharfstein, J. and Greene, J., The Pandemic and the Supply Chain: Gaps in Pharmaceutical Production and Distribution. American Journal of Public Health, 2021; 111: 635-639. https://doi.org/10.2105/AJPH.2020.306138.
13. Jordan, Debbie, *"An overview of the Common Technical Document (CTD) regulatory dossier" (PDF).* Medical Writing, 2014; 23(2): 102.
14. Nordfjeld, K. and Strasberger, V., Creating ECTD Applications. Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector, 2006; 3: 140-146. https://doi.org/10.1057/palgrave.jgm.4940111
15. Nakai, K., Araki, Y., Ebina, D., Watanabe, T., Tanaka, Y. and Toyoshima, S., Electronic Common Technical Document Implementation in Japan. Drug Information Journal, 2009; 43: 395-401. https://doi.org/10.1177/009286150904300402
16. Suchanek, A. and Ostermann, H., The Electronic Common Technical Document (ECTD): An International Pro/Con Analysis of the Pharmaceutical Product Electronic Submission Process. Drug Information Journal, 2012; 46: 124-139. https://doi.org/10.1177/0092861511427871
17. Phillips, V., The Changing Role of Regulatory Operations. Regulatory Rapporteur, 2022; 19: 10-23.
18. Research, Center for Drug Evaluation and "Investigational New Drug (IND) Application". *FDA*, 14 November 2023.

19. *"The Drug Development Process. Step 1: Discovery and Development"*. U.S. Food and Drug Administration. January 4, 2018. *Retrieved May 1, 2018*.
20. "CDER Leadership Bios". FDA. 22 December 2022. Retrieved 24 December 2022.