Journal of Modern Techniques in Biology and Allied Sciences
This Content Available at www.lapinjournals.com ISSN (O): 3048-9970
(An International online peer reviewed Journal)
Review Article Open Access

REGULATORY AFFAIRS AND REGULATORY REQUIREMENTS FOR NEW DRUG APPROVAL

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Article History: Received: 22 Apr 2025, Revised: 08 May 2025, Accepted: 19 May 2025, Published: 25 June 2025

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DOI: https://doi.org/10.70604/jmtbas.v2i1.52

Abstract
Regulatory affairs is a growing field dedicated to ensuring the safety, quality, and efficacy of drug products through the submission of Investigational New Drug (IND) and New Drug Applications (NDA) to regulatory authorities. This process is critical for safeguarding public health by preventing the distribution of harmful or ineffective drugs. The primary goal of regulatory affairs professionals is to manage and oversee clinical and nonclinical trials, ensuring compliance with the necessary guidelines before a drug reaches the market. Different countries have varying regulatory requirements for marketing authorization, with each country's regulatory authority responsible for enforcing these standards. In India, for example, the Central Drugs Standards Control Organization (CDSCO) is the key body responsible for approving new drugs. This review highlights the regulatory process for new drug approval in India, detailing the steps and documentation required for IND and NDA submissions. Furthermore, it discusses the importance of post-marketing surveillance (Phase IV) to monitor the long-term safety of approved drugs. The regulatory frameworks and processes, though similar in some respects, vary across regions like the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and CDSCO, with each playing a crucial role in the global drug approval landscape.

Keywords: Regulatory affair, Safety, Efficacy, Clinical investigation, Drug approval, And Regulatory requirements.

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Introduction
Regulatory affairs professionals play a vital role throughout a product's lifecycle, from development to post-market surveillance. They work closely with research, manufacturing, and marketing teams to ensure compliance with evolving regulatory standards. Effective regulatory strategies can expedite product approvals and minimize risks associated with non-compliance. With globalization, RA experts must navigate diverse regulatory frameworks across different regions. Ultimately, their expertise helps bring safe, high-quality, and innovative healthcare products to patients worldwide [1].

Regulatory affairs (RA) are a career opportunity within regulated industries such as pharmaceuticals, medical devices, veterinary medicine, cosmetics, and more. RA serves as a crucial bridge between pharmaceutical companies and government authorities, ensuring the efficacy and safety of medicinal products and overseeing the registration process, which is why it is often referred to as "government affairs." In the world of drug development, regulatory affairs are a profession where one false move can jeopardize years of research and data. Therefore, RA professionals must thoroughly understand the relevant information and be proficient in both the technical (hardware) and strategic (software) aspects of their role. Most companies whether major multinational pharmaceutical corporations or small biotechnology firms have specialized departments staffed with regulatory affairs professionals [2].

Different countries have specific regulatory requirements for the approval of new drugs, making it difficult to adopt a single regulatory approach for a Marketing Authorization Application (MAA) across multiple regions. As a result, understanding each country's regulatory framework is essential. The United States (US) and the European Union (EU) are major markets, attracting significant attention to their pharmaceutical regulations. Once a lead molecule is identified and optimized,

preclinical trials are conducted, followed by clinical studies after obtaining approval from the relevant authority. Clinical trials progress through four phases to ensure the drug's safety, efficacy, and optimal dosing. Upon successful completion, an MAA or a New Drug Application (NDA) is submitted for marketing approval, supported by preclinical and clinical data [3, 4].

Different phases of clinical trials

Pre-clinical study

- Phase I - Clinical trial
- Phase II - Exploratory trial
- Phase III- Confirmatory trial
- Phase IV- Post Marketing trial.

After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application. At the conclusion of the review of an NDA, there are 3 possible actions that can send to sponsor:

- Not approvable- in this letter list of deficiencies and explain the reason.
- Approvable - changes and possible request commitment to do post-approval studies.
- Approval- it state that the drug is approved If the action taken is either an approvable or a not approvable, then the regulatory body provides applicant with an opportunity to meet with agency and discuss the deficiencies.[5]

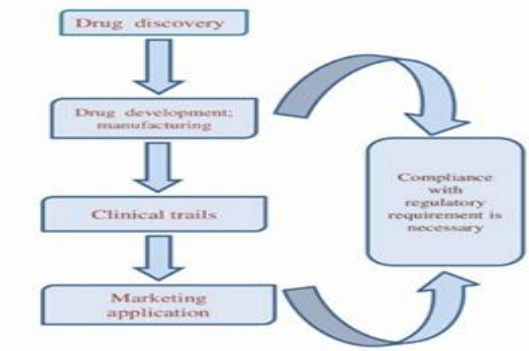

Figure 1: Regulation of Drug Approval Process

1. Historical Overview of Regulatory Affairs

The regulatory affairs department can be established based on government desires. And for regulating the severe adverse consequences in public health. Actually, regulatory affairs can act as interphone between pharmaceutical industry and regulatory body. During 1950's there was many disasters were happened due to the invalid judgement of professionals. During the manufacturing and incidence of adulteration of drug substances which cause death of patients. So due to this after this incident the government was thinks to establish the regulatory bodies which give new regulations related on quality, safety, efficacy of new drug products [6].

1.1 Disasters out of India:

In 1935, a tragedy involving the oral elixir of sulphanilamide, prepared with the toxic solvent diethylene glycol, led to the deaths of over 100 people, highlighting the dangers of unregulated drug formulations. In response, the U.S. government passed the Food, Drug, and Cosmetic Act of 1938, empowering the FDA to approve drugs for safety before public distribution. A few decades later, between 1961 and 1962, the thalidomide disaster further exposed regulatory gaps when the drug, used to treat morning sickness, caused severe birth defects in over 10,000 children and led to hundreds of deaths. These two tragedies underscored the urgent need for rigorous drug testing, especially for vulnerable populations like pregnant women. They triggered major reforms in drug approval processes, establishing stringent preclinical and clinical trial requirements and shaping modern pharmaceutical regulations to prioritize patient safety [7].

1.2 History of Regulatory Affairs in India

Till 20th century the pharmaceutical products import from other countries, so after world war- 1 in 1914. Due to increased demand for the drug products, many substandard drug products enter into market, to control these products, many legislations were made from time to time (Table: 1) [8, 9].

Table 1: List of Regulatory authorities in different countries

COUNTRY	AUTHORITY
India	Central Drug Standard Control Organization (CDSCO)
United States of America (USA)	Food And Drug Administration (FDA)
Japan	Pharmaceutical and Medical Devices Agency (PMDA)
Australia	Therapeutic Goods Administration (TGA)
Canada	Health Canada
France	National Agency for the Safety of Medicine and Health Products (ANSM)
Germany	Federal Institute for Drugs and Medical Devices
Greece	National Organization for Medicines
China	National Medical Products Administration
Europe	European Medicine Agency
Pakistan	Drug Regulatory Authority of Pakistan
Malaysia	National Pharmaceutical Regulatory Agency (NPRA)
Saudi Arabia	The Saudi Food and Drug Authority (SFDA)
UAE	The UAE Ministry of Health (MOH)
Philippines	The Food and Drug Administration
Bangladesh	Directorate General of Drug Administration (DGDA)
Israel	Ministry of Health
Nepal	Department of Drug Administration
South Korea	The Ministry of Food and Drug Safety (MFDS)
Hungary	National Institute of Pharmacy and Nutrition

2. List of International Regulatory Authorities

1. WHO -World Health Organization
2. ICH - International Council for Harmonization
3. WIPO- World Intellectual Property Organization

3. National Regulatory Authority

India: Central Drug Standard Control Organization (CDSCO). Drug Controller General of India (DCGI)

US: - Food and Drug Administration (USFDA)

Europe: - European Directorate for Quality of Medicine (EDQM)

European medicine evolution agency (EMEA). To streamline the regulatory framework and decision-making processes of the Drug Controller General of India (DCGI), several committees have been established. Key among them is the Drugs Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC), which oversee the regulation of both Modern Scientific Medicine and Indian Traditional Medicine. The Central Drug Laboratory

at the Central Research Institute in Kasauli, Himachal Pradesh, also supports drug testing efforts. The DTAB, comprising technical experts, advises central and state governments on technical matters and reviews proposed amendments to the Drugs and Cosmetics Act. Meanwhile, the DCC, which includes officials from central and state drug control departments, ensures the consistent implementation of drug regulations across India. These structured bodies strengthen the regulatory system, enhancing oversight of both modern and traditional medical practices [10].

A) **Health Authority (HA)**

The health authority plays a vital role in creating regulatory guidelines to ensure pharmaceutical products meet safety, efficacy, and quality standards. It works with international bodies like WHO and ICH to harmonize regulations globally. Coordination with industry stakeholders helps shape practical and feasible regulatory requirements. Through this collaboration, the health authority balances strict oversight with the need to promote innovation. Clear marketing authorization processes guide pharmaceutical companies in bringing safe and effective drugs to market.

B) **Pharmaceutical Industry**: According to regulatory necessity of quality, safety and efficacy of manufacturer develops drugs and applies for market Authorization.

4. Role of Regulatory Affairs

- It is a unique combination of Science and Management.
- It is the first point of contact between pharmaceutical company and Regulatory Authority. • It helps in knowing legislations implementing legislations and get approval for the legislations Authorities. Laid down by Regulatory

4.1. In Production

- Role of Regulatory Affairs started from product development to marketing, marketing to post marketing surveillance.
- Regulatory Affairs give advises at all stages with respect to technical requirements.
- Regulatory Affairs should ensure the labelling and packing of drug product

4.2. In Clinical Studies

It should collect analyses and communicate the obtained data to Regulatory Authorities for approval

4.3. In Research and Development

It should work together with Research and Development and marketing to develop novel drug product by using latest technologies and Regulatory Development

4.4 In Quality Control and Quality Assurance

In collaboration with QC and QA the Regulatory Authorities should submit the Dossier (documentation containing all details) which includes

1. Certificate of Analysis
2. Stability studies
3. Analytical Method Validation Report
4. Process Validation Report
5. Master Formula Record to Regulatory Authorities for approval.

4.5. In licensing

Regulatory Affairs should all the supporting documents to Regulatory Authorities for licensing/approval.

5. Drug Approval Process in India

The Drug and Cosmetic Act of 1940, along with the 1945 Rules, was enacted by the Indian Parliament to regulate the import, manufacture, distribution, and sale of drugs and cosmetics. To implement these regulations effectively, the Central Drugs Standard Control Organization (CDSCO) and the position of the Drugs Controller General of India (DCGI) were established. In 1988, Schedule Y was added to the Rules to provide guidelines for clinical trials, later revised in 2005 to align with international standards. Companies wishing to manufacture or import new drugs in India must submit an application in Form 44, along with clinical trial data as per Schedule Y, demonstrating the drug's safety and efficacy for the Indian population [11, 12].

It is given in THREE phases:

First phase

1. Applicant is filling the application of IND (Investigational New Drug) with their informational studies to CDSCO headquarters.
2. All the information is examined by new drug division.
3. Then detailed review by IND committee.
4. With proper information of CDSCO – Recommendation to DCGI (Drug Controller General of India).
5. Then IND application is approved.

Second Phase

1. Application is given one copy of IND information to ethical committee with application.
2. Then ethical committee reports the application of IND.
3. This process taken within 12 Weeks.

Third Phase

1. In 1st phase, IND application is approved and in 2nd phase, ethical committee report is positive then 3rd phase is started.
2. In 3rd phase, clinical trials are started.
3. Then again give application for new drug registration to CDSCO.
4. Then finally review by DCGI.
5. If Review is positive or complete then LICENSE IS GRANTED.
6. If Review is not complete then refused to grant license [13, 14,].

5.1 New Drug Application (NDA)

A New Drug Application (NDA) is a formal submission to the U.S. Food and Drug Administration (FDA) seeking approval to market a new drug. It compiles all data from the drug's development, including preclinical studies,

clinical trial results, manufacturing processes, and proposed labelling. The NDA provides a full profile of the drug's safety, efficacy, pharmacokinetics, and pharmacodynamics. After submission, the FDA has 60 days to determine if the application is complete before proceeding with a detailed review. If the benefits outweigh the risks, the FDA grants approval, allowing the drug to be marketed in the U.S. [15]. Contents and Format of NDA Two copies of the application are: (a) Archival copy and **(B) Review Copy.**

a) Archival Copy: It serves as a reference source for FDA reviewers to locate information not contained in the review copy; and it contains copies of tabulations and clinical study case report forms. It contains the following elements:

b) Application form FDA 356
c) Index
d) Summary
e) Technical sections: further typed to
f) Chemistry, manufacturing and controls section
g) Non-clinical pharmacology and toxicology section
h) Human pharmacokinetics and bioavailability section
i) Microbiology section
j) Clinical data section
k) Statistical section
l) Pediatric use section
m) Samples and labeling
n) Case report forms

b.) Review Copy: Each technical section is separately bound in each folder. Each technical sect ion should contain:

1. Index
2. Copy of FDA Form 356 h
3. Copy of cover letter
4. Letters of authorization
5. Copy of application summary

The FDA can conduct meetings with the sponsor at least two times; once at the end of Phase 2 clinical trials and another before an NDA is submitted i.e., a pre- NDA meeting. The review team shall study the study results and make a decision whether or not to approve the application (Figure 2)

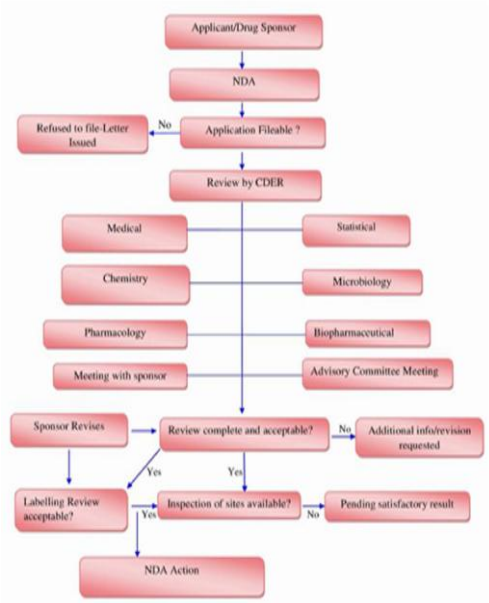

Figure 2: New Drug Application (NDA).

5.2 Abbreviated New Drug Application (ANDA)

ANDA is applied for products with same or closely related active ingredients, dosage form, and strength, route of administration, use and labelling as product already shown to be safe and effective. It is used when the patent has expired for a product, and a company wants to market its copy. Such drugs are called generic drugs, which should meet bio and pharmaceutical equivalent standards [16]. An ANDA is submitted to Center for Drug

Evaluation and Research, Office of Generic Drugs, where it is reviewed and approved. Content and Format of ANDA

1. Application form
2. Table of contents
3. Basis for ANDA submission
4. Conditions of use
5. Active ingredients
6. Route of administration, dosage from, strength Bioequivalence
7. Labelling
8. Chemistry, manufacturing and control
9. Human pharmacokinetics and bioavailability
10. Samples
11. Analytical methods
12. Case report forms and tabulations.

The Division of Bioequivalence's Office of Generic Drugs issued guidance in 1992 on valid statistical analysis for bioequivalence studies. Later, the FDA released draft guidance for studies comparing pharmacokinetic metrics in INDs, NDAs, and ANDAs. Approved branded and generic drugs are listed in the FDA's "Orange Book," which evaluates safety, effectiveness, and therapeutic equivalence. (Figure 3) [17,18].

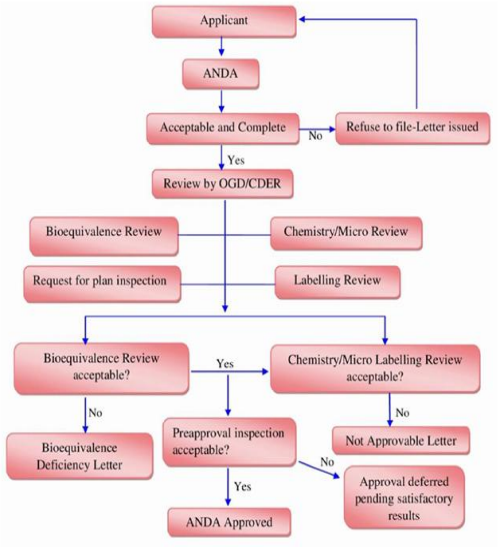

Figure 3: Abbreviated New Drug Application (ANDA).

5.3 Supplemental New Drug Application (SNDA)

After approval of NDA or ANDA, all significant changes in the conditions described in the applications must be approved, by filing a supplemental NDA or ANDA. Such changes like those in packing or ingredients should be approved by the CDER. New-uses approvals of already approved drugs coming under this category are a better innovation as they need lesser resources to review than that needed for original-use approvals

Conclusion

Regulatory affairs play a vital role in helping pharmaceutical companies navigate complex and evolving global regulations. Professionals in this field manage submissions like INDs and NDAs, ensuring compliance from early development through post-market surveillance. Clinical trials, critical to drug approval, provide essential data on safety and efficacy, forming the foundation for regulatory review. While efforts to harmonize standards exist, regional differences still require companies to meet specific requirements in each market. Despite these challenges, global regulatory cooperation helps maintain high safety standards and supports the development of new therapies worldwide.

Author Contributions

All authors are contributed equally

Financial Support

None

Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

Acknowledgements

None

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