Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/qq3efp90

CURRENT APPROVAL PROCEDURE FOR NEW REGULATIONS, STANDARDS, POLICIES & GUIDENCE ISSUED BY REGULATORY AUTHORITES

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ABSTRACT
A regulatory cycle, by which an individual/association/support/pioneer gets approval to send off a medication in the market, is known as drug approval process. As a general rule, a drug approval process contains different stages: application to conduct clinical preliminaries, directing clinical preliminaries, application to promoting approval of drug and post-showcasing studies. Each nation has its own regulatory power, which is dependable to authorize the standards and guidelines and issue the rules to manage the marketing of the drugs. This article will concentrate the similarities and contrasts in drug approval process of different regulatory bodies.

INTRODUCTION
The role of the regulatory affairs department[1]
The regulatory affairs (RA) department of a pharmaceutical company is responsible for obtaining approval for new pharmaceutical products and ensuring that approval is maintained for as long as the company wants to keep the product on the market. It serves as the interface between the regulatory authority and the project team, and is the channel of communication with the regulatory authority as the project proceeds, aiming to ensure that the project plan correctly anticipates what the regulatory authority will require before approving the product. It is the responsibility of RA to keep abreast of current legislation, guidelines and other regulatory intelligence. Such rules and guidelines often allow some flexibility, and the regulatory authorities expect companies to take responsibility for deciding how they should be interpreted. The RA department plays an important role in giving advice to the project team on how best to interpret the rules. During the development process sound working relations with authorities are essential, e.g. to discuss such issues as divergence from guidelines, the clinical study programme, and formulation development.
Most companies assess and prioritize new projects based on an intended Target Product Profile (TPP). The RA professional plays a key role in advising on what will be realistic prescribing information (‘label’) for the intended product. As a member of the project team RA also contributes to designing of the development programme. The RA department reviews all documentation from a regulatory perspective, ensuring that it is clear, consistent and complete, and that its conclusions are explicit. The department also drafts the core prescribing information that is the basis for global approval, and will later provide the platform for marketing. The documentation includes clinical

trials applications, as well as regulatory submissions for new products and for changes to approved products. The latter is a major task and accounts for about half of the work of the RA department.

Function of Regulatory Agencies

The pharmaceutical industry is one of the utmost regulated industry globally composing of numerous different regulations; the main challenges of drug regulatory agencies are to guarantee safety, efficacy, and quality of drug. Now regulatory agencies are playing a vital role in all the aspects of drug development like production, storage, sales, import, distribution, and supply of drug.

The major functions of the global regulatory affairs agencies involve:

- Offer support on development of product, manufacturing, registration, and marketing: once the applicant applies for the registration, the regulatory agency starts verbal and paper communication to the applicant and signifying them for improved documentation and clinical practices which diminish countless chances of mistakes.
- Informing strategic regulatory controls and providing the worldwide regulatory policy for product development, manufacturing, and registration: It aids the applicant to advance a product which is accepted universally.
- Developing and maintaining a dependable relationship with regulatory authorities through effective verbal and written communication during reply and response to queries arising during new drug application (NDA)/investigational new drug application (INDA)/abbreviated new drug application (ANDA) filing. Groundwork, maintenance, and scheduled appraisal of standard operating procedures, batch manufacturing records, dossiers, temperature control documents, and other documents: it ensures the product quality.
- Development of proper tag and leaflets like summary of product characteristics, patient information, etc.
- The regulatory agency has to establish standard formats for the development of appropriate labels of each developed drug: to confirm all required information is given on the product, e.g., date of manufacturing, expiry date, and ingredients.
- To complete record data of company's product and maintain the records of therapeutic products in agreement with current regulations and guidelines.
- To maintain reports and assemble information concerning adverse drug reactions of any product and to help the research and development department to overcome it. For example, assemblage of data by pharmacovigilance division can be used to overcome the adverse drug reactions and for data collection, the leadership is provided by regulatory agencies.
- To prepare data about new product for doctors and other healthcare professionals for harmless and effective practice of medicine and maintain records, reports of post-marketing surveillance of new product. It also helps to prepare the leaflets and advertising material for existing as well as new drugs
- Deliver continuous training to the associated personnel for maintenance of records and reports, for pilot plant, research, and developments. It may be noted that this record helps the organization with routine production and for complying to standard operating procedures to facilitate the audits and inspections.

All pharmaceutical establishments have to obey the regulations made by health authorities. These regulations not only assure good quality of product but also assure public health and safety. Hence, the regulatory agencies should be designed with a significant understanding of the local and global regulatory scenario and functions one step ahead, for this purpose the agency needs a technically skillful team to impose standard regulations. Nowadays the agencies are also working for the harmonization around the globe for more detailed regulation which also supports the innovator to develop drug products with global acceptability.

Product development should fulfill regulatory requirements and good regulatory practices.

An important proactive task of the RA is to provide input when legislative changes are being discussed and proposed. In the ICH environment there is a greater possibility to exert influence at an early stage.[1]

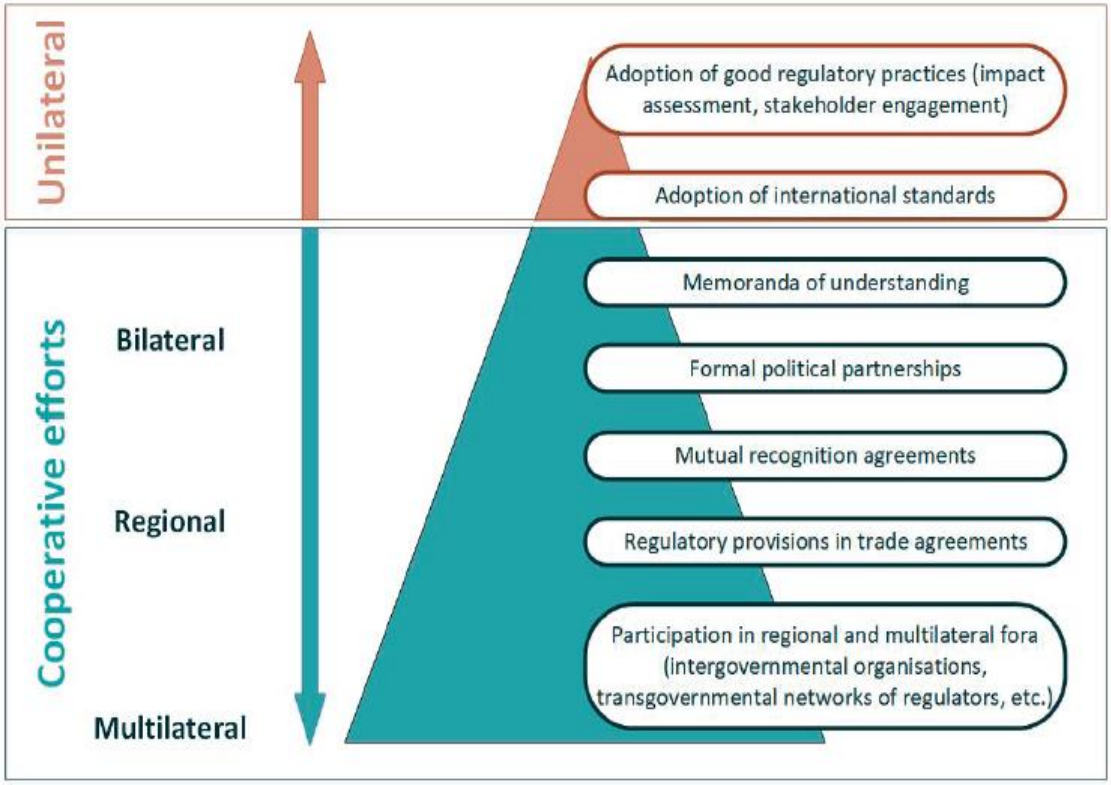

Fig 1 : The role of regulatory Agency

National health authorities have the duty to ensure that available pharmaceutical products,whether imported or manufactured locally,are of good quality,safe and efficacious.This is particularly difficult for vaccines and biological products,the quality of which cannot be established entirely by tests on the material in the final container.A national control authority should therefore be established that is responsible for ensuring that the manufacturer is adhering to approved standards of good manufacturing practice and quality assurance specific to the product.The procedures through which the national control authority confirms the assurance of quality provided by the manufacturer will depend on the resources avalible and whether the product is manufactured locally or imported.

In general,biological products are distinguished from other drugs by being derived from living organisms(ranging from normal or genetically modified microorganisms to fluids and tissues derived from various animal and human sources) and frequently have a complex molecular structure.They require special quality considerations because of the biological nature of:(a) the starting materials; and /or (b) the manufacturing process;and/or (c)the test methods needed to characterize batches of the product.

Development in biological products have been extremely rapid in recent years,and the potential valve of such products in improving health care on a global scale is immense.There is an urgent need to match technological advances with appropriate mechanisms for assuring the safety,quality and efficacy of the products[2].

Laws & Regulations

The Basics of the Regulatory Process

Regulations are mandatory requirements that can apply to individuals, businesses, state or local governments, non-profit institutions, or others.

Congress passes the laws that govern the United States, but Congress has also authorized EPA and other federal agencies to help put those laws into effect by creating and enforcing regulations.
A basic description of how laws and regulations are developed, what they are, and where to find them, with an emphasis on environmental laws and regulations.

- Creating a law
- Putting the law to work
- Creating a regulation
- How you can get involved

Creating a law

Step 1: Congress Writes a Bill

A member of Congress proposes a bill. A bill is a document that, if approved, will become law. To see the text of bills Congress is considering or has considered, go to Congress.gov

Step 2: The President Approves or Vetoes the Bill

If both houses of Congress approve a bill, it goes to the President who has the option to either approve it or veto it. If approved, the new law is called an act or statute. Some of the better-known laws related to the environment are the Clean Air Act, the Clean Water Act, and the Safe Drinking Water Act.

- Summaries of the laws EPA administers
- Congress.gov: for more information about the legislative process

Step 3: The Act is Codified in the United States Code

Once an act is passed, the House of Representatives standardizes the text of the law and publishes it in the United States Code (U.S.C.). The U.S.C. is the codification by subject matter of the general and permanent laws of the United States. Since 1926, the U.S.C. has been published every six years. In between editions, annual cumulative supplements are published in order to present the most current information.

United States Code: This database is available from the Government Printing Office (GPO). GPO is the sole agency authorized by the federal government to publish the U.S.C.

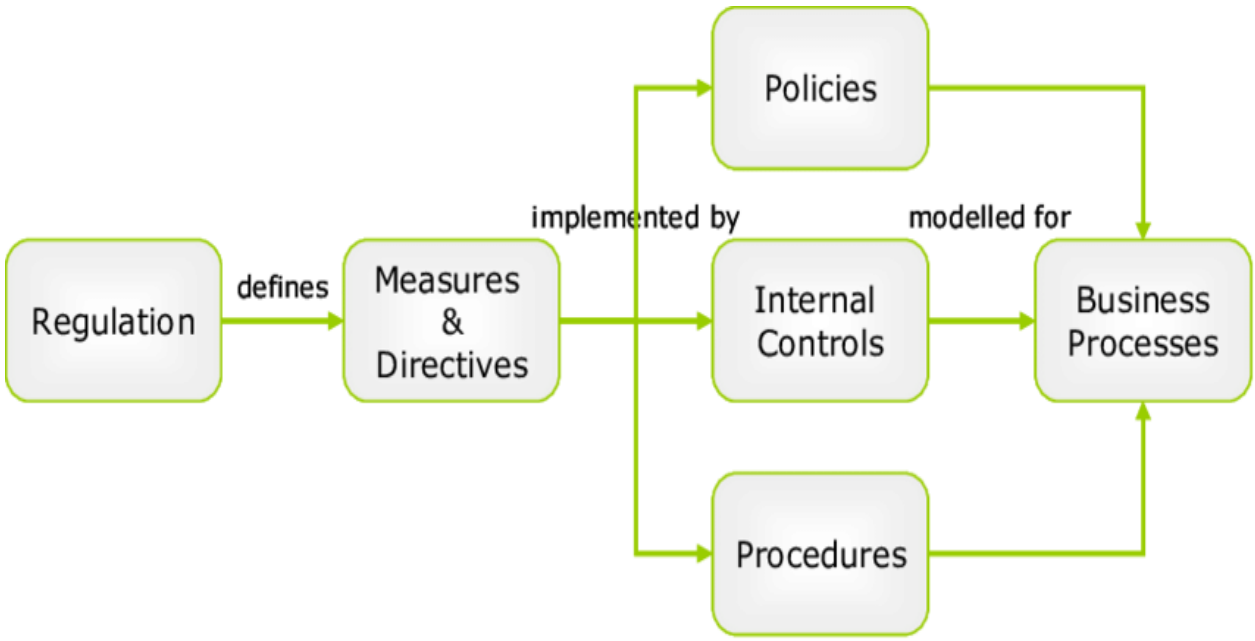

Fig 2: Basics for regulatory process

Putting the law to work

Once a law is official, here's how it is put into practice: Laws often do not include all the details needed to explain how an individual, business, state or local government, or others might follow the law. The United States Code would not tell you, for example, what the speed limit is in front of your house. In order to make the laws work on a dayto- day level, Congress authorizes certain government agencies - including EPA – to create regulations.

Regulations set specific requirements about what is legal and what isn't. For example, a regulation issued by EPA to implement the Clean Air Act might explain what levels of a pollutant - such as sulfur dioxide - adequately protect human health and the environment. It would tell industries how much sulfur dioxide they can legally emit into the air, and what the penalty will be if they emit too much. Once the regulation is in effect, EPA then works to help Americans comply with the law and to enforce it.

- Find out more about Compliance.
- Learn more about Enforcement.

Creating a regulation

When developing regulations, the first thing we do is ask if a regulation is needed at all. Every regulation is developed under slightly different circumstances, but this is the general process:

Step 1: EPA Proposes a Regulation

The Agency researches the issues and, if necessary, proposes a regulation, also known as a Notice of Proposed Rulemaking (NPRM). The proposal is listed in the Federal Register (FR) so that members of the public can consider it and send their comments to us. The proposed rule and supporting documents are also filed in EPA's official docket on Regulations.gov.

Step 2: EPA Considers Your Comments and Issues a Final Rule

Generally, once we consider the comments received when the proposed regulation was issued, we revise the regulation accordingly and issue a final rule. This final rule is also published in the FR and in EPA's official docket on Regulations.gov.

Step 3: The Regulation is Codified in the Code of Federal Regulations

Once a regulation is completed and has been printed in the FR as a final rule, it is codified when it is added to the Code of Federal Regulations (CFR). The CFR is the official record of all regulations created by the federal government. It is divided into 50 volumes, called titles, each of which focuses on a particular area. Almost all environmental regulations appear in Title 40. The CFR is revised yearly, with one fourth of the volumes updated every three months. Title 40 is revised every July 1.

- Code of Federal Regulations database - a searchable database of the entire CFR from GPO.

How you can get involved

Go to the "Get Involved with EPA Regulations" page to learn how you can comment on our regulations and keep tabs on rulemakings.[3]

Regulatory Issues in the Indian Pharmaceutical Industry

This section undertakes a review and assessment of regulatory issues in the Indian pharmaceutical industry. Understanding the regulatory scenario in this sector is extremely crucial not only due to the rapid and ongoing changes at the global level, largely with reference to good manufacturing practices (GMP), good clinical practices (GCP) and good laboratory practices (GLP) but also due to the onus on the regulatory bodies to ensure a healthy supply of quality drugs at affordable prices to the Indian masses.

The present section begins with a brief description of the major regulatory bodies monitoring the Indian pharmaceutical sector. It then undertakes a review of the prevailing mechanisms for drug regulation and temporal progression of some predominant policy measures and Acts. The section subsequently provides a comprehensive account of the status and key guidelines pertaining to the

dimensions of drug pricing, patent related issues, GMP and clinical trials, in addition to a brief review of standards for medical devices and biotech products. It concludes with an assessment of the deficiencies of present regulatory regime and some new initiatives by the State to ensure the production and marketing of safe and efficacious drugs at affordable prices in the domestic sphere and to sustain current growth prospects in the global markets.

Major bodies regulating drugs and pharmaceuticals

The principal regulatory bodies entrusted with the responsibility of ensuring the approval, production and marketing of quality drugs in India at reasonable prices are:

The Central Drug Standards and Control Organization (CDSCO), located under the aegis of the Ministry of Health and Family Welfare. The CDSCO prescribes standards and measures for ensuring the safety, efficacy and quality of drugs, cosmetics, diagnostics and devices in the country; regulates the market authorization of new drugs and clinical trials standards; supervises drug imports and approves licences to manufacture the above-mentioned products;

The National Pharmaceutical Pricing Authority (NPPA), which was instituted in 1997 under the Department of Chemicals and Petrochemicals, which fixes or revises the prices of decontrolled bulk drugs and formulations at judicious intervals; periodically updates the list under price control through inclusion and exclusion of drugs in accordance with established guidelines; maintains data on production, exports and imports and market share of pharmaceutical firms; and enforces and monitors the availability of medicines in addition to imparting inputs to Parliament in issues pertaining to drug pricing.

The Department of Chemicals and Petrochemicals also oversees policy, planning, development and regulatory activities pertaining to the chemicals, petrochemicals and pharmaceutical sector. The responsibilities assumed by this body are relatively broader and varied in comparison to the other two bodies. The main aspects of pharmaceutical regulation are thus divided between the above two ministries. The Ministry of Health and Family Welfare examines pharmaceutical issues within the larger context of public health while the focus of the Ministry of Chemicals and Fertilizers is on industrial policy. However, other ministries also play a role in the regulation process. These include the Ministry of Environment and Forests, Ministry of Finance, Ministry of Commerce and Industry and the Ministry of Science and Technology. The process for drug approval entails the coordination of different departments, in addition to the DCGI, depending on whether the application in question is for a biological drug or one based on recombinant DNA technology. Issues related to industrial policy such as the regulation of patents, drug exports and government support to the industry are governed by the Department of Industrial Policy and Promotion and Directorate General of Foreign Trade, both under the aegis of Ministry of Commerce and Industry and the Ministry of Chemicals and Fertilizers. With respect to licencing and quality control issues, market authorization is regulated by the Central Drug Controller, Ministry of Health and Family Welfare, Department of Biotechnology, Ministry of Science and Technology (DST) and Department of Environment, Ministry of Environment and Forests. State drug controllers have the authority to issue licences for the manufacture of approved drugs and monitor quality control, along with the Central Drug Standards Control Organization (CDSCO).[4]

Prevailing Mechanisms

This sub-section primarily focuses on major regulatory policies and mechanisms in relation to drug pricing and development of standards for ensuring safety and efficacy.

In India, drug manufacturing, quality and marketing is regulated in accordance with the Drugs and Cosmetics Act of 1940 and Rules 1945. This act has witnessed several amendments over the lastfew decades. The Drugs Controller General of India (DCGI), who heads the Central Drugs Standards Control Organization (CDSCO), assumes responsibility for the amendments to the Acts and Rules. Other major related Acts and Rules include the Pharmacy Act of 1948, The Drugs and Magic Remedies Act of 1954 and Drug Prices Control Order (DPCO) 1995 and various other policies instituted by the Department of Chemicals and Petrochemicals.

Some of the important schedules of the Drugs and Cosmetic Actsi include: Schedule D: dealing with exemption in drug imports, Schedule M: which, deals with Good Manufacturing Practices involving premises and plants and Schedule Y: which, specifies guidelines for clinical trials, import and manufacture of new drugs

In accordance with the Act of 1940, there exists a system of dual regulatory control or control at both Central and State government levels. The central regulatory authority undertakes approval of new drugs, clinical trials, standards setting, control over imported drugs and coordination of state bodies' activities. State authorities assume responsibility for issuing licenses and monitoring manufacture, distribution and sale of drugs and other related products.

The Patents Act of 1970, Drug Price Control Order 1970 and ForeignExchange Regulation Act 1973 played a significant role in terms of the building of indigenous capability with regard to manufacture of drugs. The New Drug Policy of 1978 provided an added thrust to indigenous self-reliance and availability of quality drugs at low prices.

DPCO 1987 heralded the increasing liberalization in the industry. One of the important features of this act was the reduction of the number of drugs under price control to 143.

The major objective of DPCO 1995 was to decrease monopoly in any given market segment, further decrease the number of drugs under price control to 74 and the inclusion of products manufactured by small scale producers under price control list.

In 1997, the National Pharmaceutical Pricing Authority was constituted in order to administer DPCO and deal with issues related to price revision.

The Pharmaceutical Policy 2002 carried forward earlier governmental initiatives in terms of ensuring quality drugs at reasonable prices, strengthening of indigenous capability for cost-effective production, reducing trade barriers and providing active encouragement to in-house R&D efforts of domestic firms.

AIM AND OBJECTIVE

- The aim is to provide guidance for newly developing national control authorities that may have limited resources to license and regulate biological products, including vaccines. It describes the responsibilities of such authorities and manufacturers and provides references to relevant WHO publications relating to their structure and activities. References to more detailed technical requirement published by WHO, specific for various products including vaccines, are also provided.
- Regulations protect consumers rights, health, and safety, and ensure minimum standards for products and services. For some industries, they protect the environment. They also protect the rights of employees. Overall, they ensure that your business is achieving its goals safely and fairly.

CONCLUSION

New Drug Application (NDA) is an application submitted to the individual regulatory authority for authorization to market a new drug i.e. innovative product. To gain this permission a sponsor submits preclinical and clinical test data for analyzing the drug information, description of manufacturing trials.

Evaluating the effectiveness of pharmaceutical legislation and accompanying regulations is not always easy.The process of evaluation depends on the types of performance indicators and criteria used and on the availadility of adequate data.

The important factor in the effectiveness of pharmaceutical laws and regulations is the extent to which the legislative framework is in tune with national policy and the existing situation .Changes in policy needed to be reflected in the legislation and in its implementation.

In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, application to marketing authorization of drug and post-marketing studies.

Regulatory authority and organizations are responsible in effective drug regulation required to ensure the safety, efficacy and quality of drugs, as well as the accuracy and appropriateness of the drug information available to the public.

ACKNOWLEDGEMENT:
The Authors are thankful to Sura Labs, Dilshukhnagar, Hyderabad for providing the necessary facilities for the research work.

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