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MARKETING AUTHORIZATION PROCESS OF NEW DRUG SUBSTANCES IN U.S.A AND EUROPE

D. Sarika Prathyusha*, Brahmaiah Bonthagarala M.V. Ngabhushanam and D. Nagarjuna Reddy

Department of Pharmaceutical Management and Regulatory Affairs, Hindu College of Pharmacy, Amravati road, Guntur, A.P, India- 522002.

Abstract:

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. 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. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This work focuses on the drug approval process in India. Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article focuses on history, regulatory policy and administration, and related issues with respect to different countries like U.S.A. , Europe ,China, Australia and India.

Keywords: *USFDA, EMA, TGA, Clinical trials, Approval stage*

Corresponding Author:

D. Sarika Prathyusha ,

Department of Pharmaceutical Management and Regulatory Affairs,
Hindu College of Pharmacy, Amravati road,
Guntur, A.P, India- 522002.
E-mail: brahmaiahmph@gmail.com

QR code

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INTRODUCTION:

United States of America

USA is the major market for the pharmaceutical industry. The USA has evolved from no regulations in the 18th century to one of the highly regulated and admired regulatory authority in the world. The food and drug administration (FDA) within the U.S. Department of Health and Human Services regulates the drug approval system in United States with help of six product centers including Center for Drug Evaluation and Research (CDER)[1-5]. Drug registration in USA is majorly categorized by two types of applications: New Drug Application (NDA) and Abbreviated New Drug Application (ANDA). ANDA is filled for generic drug products; those require marketing authorization and are of exact or close copies of already approved drugs [6]. The ANDA approval process is depicted in Figure 1[7] Indeed, the way this country regulates drugs typically has been born out of adversity, out of events that have killed and injured thousands. The evolution of the current drug regulatory system in USA is recognized globally as the gold standard for drug safety and efficacy. During 1990, FDA began work to develop standards for the exchange of electronic information critical to the agency's mission. This recognized both the inefficiency of paper for transferring mass quantities of data and the need to develop a harmonized format that would be usable by FDA as well as its counterparts in the European Union and Japan. Consequently, firms are now able to submit paperless product applications and related material to world regulatory agencies more efficiently, while each review authority maintains its own high standards for product evaluation. Because all drugs have some risk, FDA task force advised the agency to make more systematic use of the principles of risk management in the way FDA oversees drug development and marketing [8-12].

TYPES OF DRUG APPLICATIONS

Investigational new drug (IND)

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA[13-16].

Introduction

1. Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

2. During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

3. FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

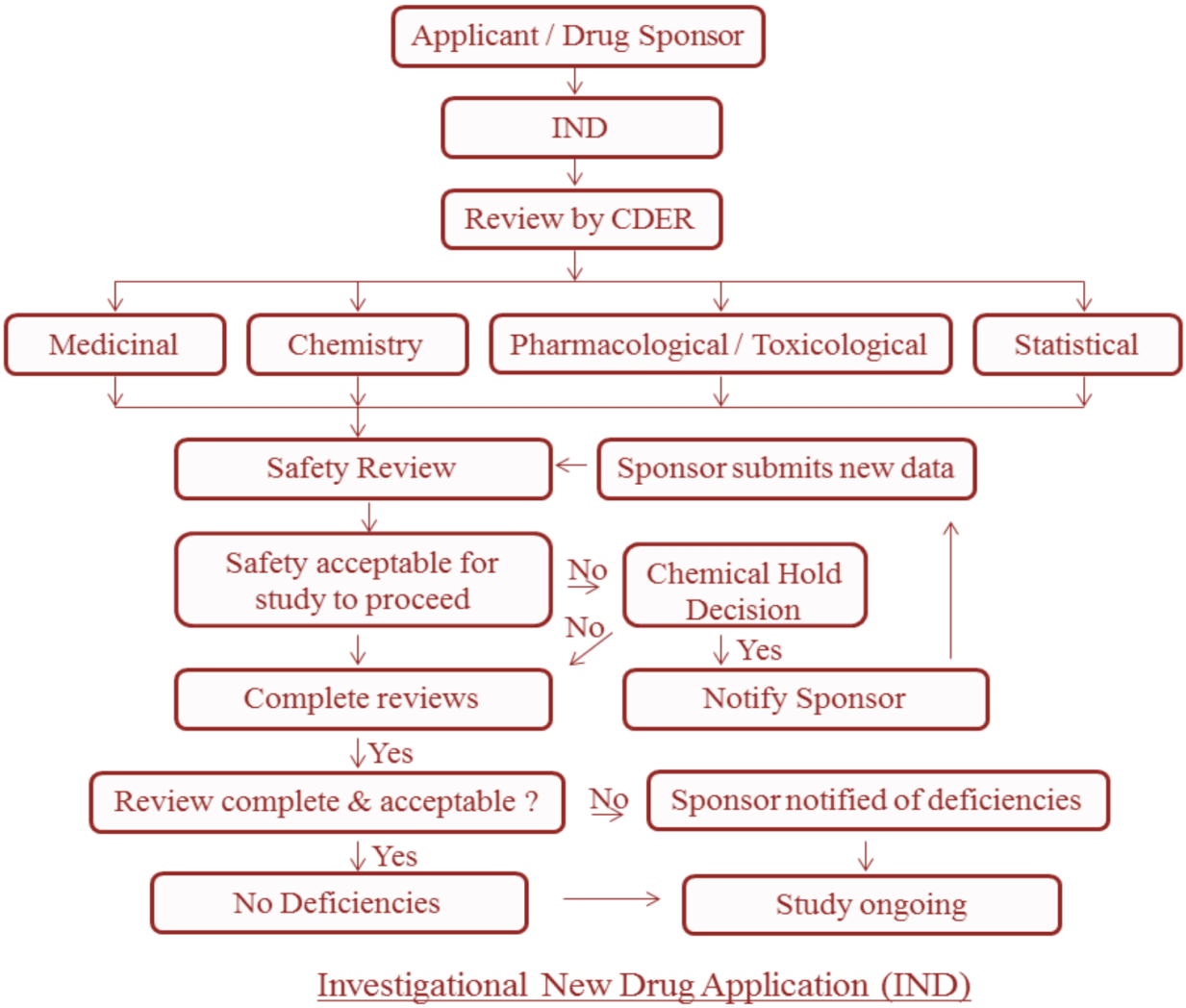
•**An Investigator IND** is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

•**Emergency Use IND** allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

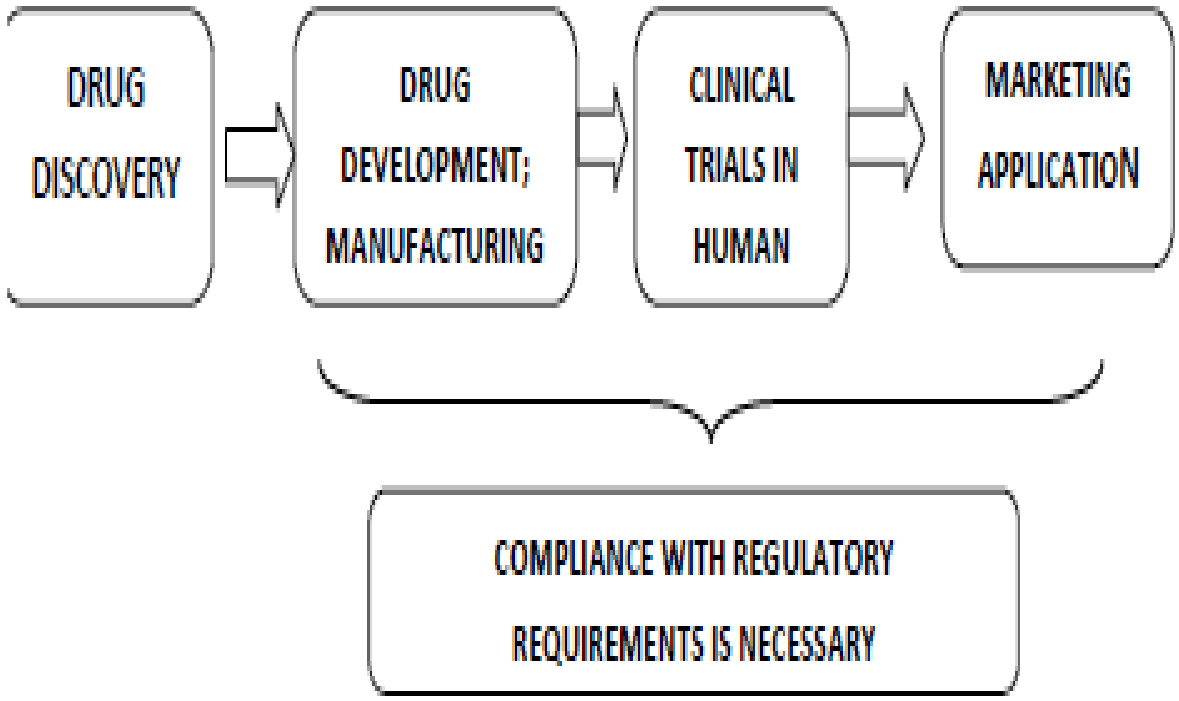
•**Treatment IND** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:
•Commercial
•Research (non-commercial)
The IND application must contain information in three broad areas:
•**Animal Pharmacology and Toxicology Studies**- Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experiences with the drug in humans (often foreign use).
•**Manufacturing Information**- Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
•**Clinical Protocols and Investigator Information**- Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations. Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

Flow chart of Investigational New Drug Application



Investigational New Drug Application (IND)



gure 2: The Basic Regulation

NEW DRUG APPLICATION (NDA)

1. When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDA's are assigned an NDA number
2. For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

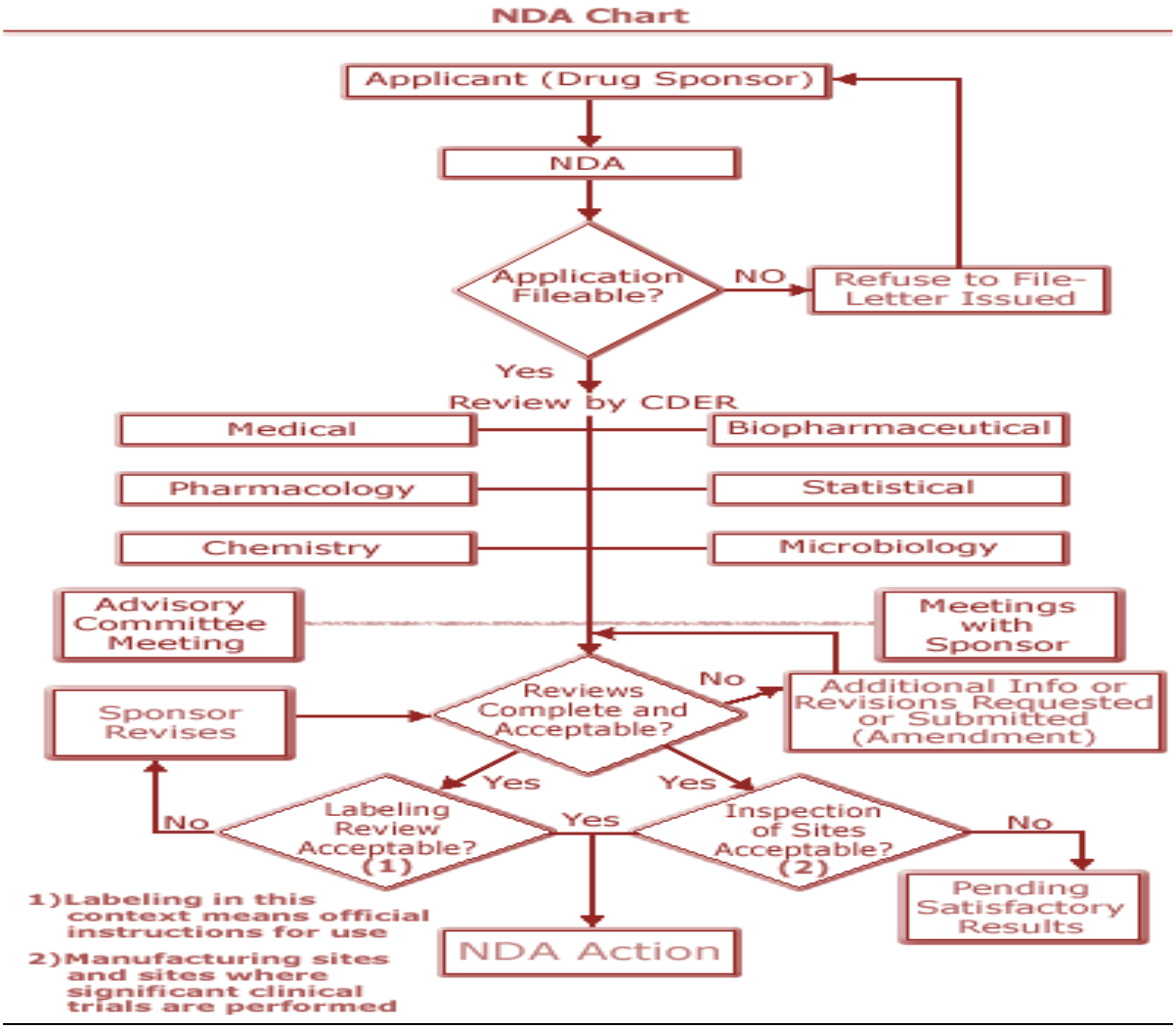
1.•Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.

2•Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.

3•Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

4.The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies,:

Flow chart of New Drug Application:



ABBREVIATED NEW DRUG APPLICATION (ANDA)

1. New drugs, like other new products, are developed under patent protection. The patent protects the investment in the drug's development by giving the company the sole right to sell the drug while the patent is in effect. When patents or other periods of exclusivity expire, manufacturers can apply to the FDA to sell generic versions. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness.

2. An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

3. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug

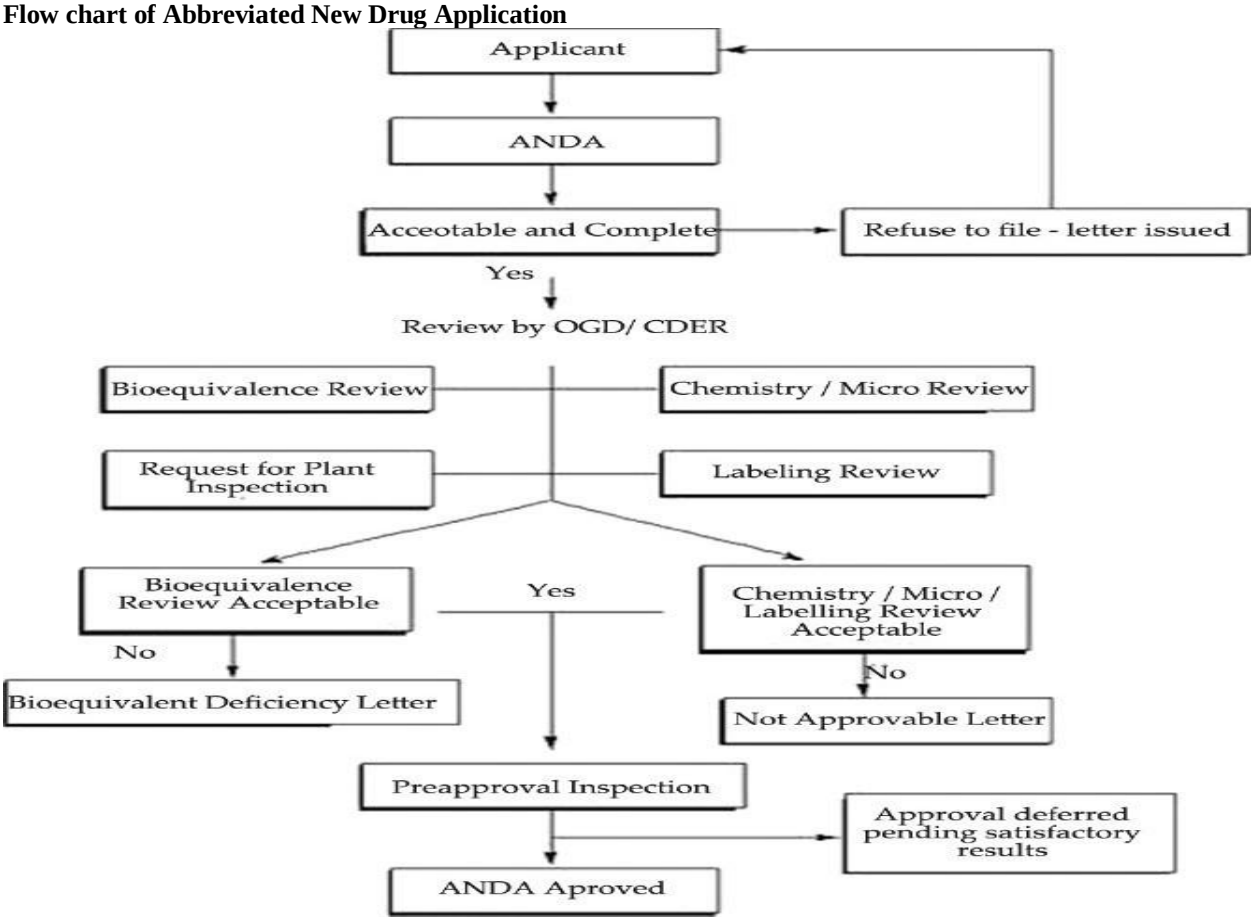
Products with Therapeutic Equivalence Evaluations (Orange Book).

4. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

5. Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Waxman-Hatch Act. This Act expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials. At the same time, the brand-name companies can apply for up to five additional years longer patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process. Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.

6. The Office of Generic Drugs home page provides additional information to generic drug developers, focusing on how CDER determines the safety and bioequivalence of generic drug products prior to approval for marketing. Generic drug application reviewers focus on bioequivalence data, chemistry and microbiology data, requests for plant inspection, and drug labeling information.

Flow chart of Abbreviated New Drug Application



European Union

INTRODUCTION

The EU has one of the most highly regarded regulatory systems in the world. The system comprises of European parliament, the council of ministers, and the European Commission. EU consists of 27 member states: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Iceland, Norway, and Liechtenstein.[8] These EFTA members are those countries which were unable to join rest of the 27 member states as common market. These three EFTA member countries along with 27 EU member states, comprises of the European Economic Area (EEA). The European Medicines Agency is a decentralized agency of the European Union, located in London.[8] The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union and applications for European marketing authorizations for both human and veterinary medicines (centralized procedure). Under the centralized procedure, companies submit a single marketing-authorization application to the Agency. Once granted by the European Commission, a centralized (or "Community") marketing authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway).

AGENCIES RESPONSIBLE

1. To market a generic medicinal product in European Economic Area (EEA) which consists of 27 member states and 3 EFTA countries, a marketing authorization has to be issued. European medicines Agency (EMA formerly known as EMEA) regulates the medicinal products marketing authorization through various committees. Different types of submissions for receiving

2. In case of Generic drug products, generally the decentralized procedure is followed whereas in case of the new drug products the application for marketing authorization is always submitted through a centralized procedure.

Agencies responsible	Procedure type	Summary
EMA	Centralized procedure	It is for single application, single evaluation and authorization allowing direct access to the single market of the member countries.
Reference member state (RMS)	Decentralized procedure (DCP)	Application is submitted to all member states where intended and choose one of them as reference member state. The assessment report is prepared by RMS including the concerned member states and based on both comments MA is granted.
Reference member state (RMS)	Mutual recognition procedure (MRP)	It is followed where an applicant having MA in one member state, wishes to obtain the same in other member states. It is based on mutual recognition of concerned member states, granted by the reference member states.
Member states	National authorization	MA is granted by Member states and hence an application must be submitted to the particular member state.

Illustrates the regulatory authorities of various countries

Name of Country/ Group	Regulatory authority
USA	FDA
EU	EMA
Canada	HPFB
Japan	PMDA
Australia	TGA
South Africa	MCC
AFRICA (Tanzania)	Independent regulatory agencies/TFDA
LATAM (Brazil)	Independent regulatory agencies/ANVISA
CIS (Russia)	Independent regulatory agencies/ ROSZDRAVNADZOR
ASIAN (Hong Kong)	Independent regulatory agencies/DOH
GCC	Independent regulatory agencies/National filling

Marketing Authorization Application (Europe)

In Europe drug approval process is regulated by European Agency for evaluation of medicinal products (EMEA),this agency gives Marketing authorization in European union.

Pharmaceutical companies can use 3 approval procedures to market their pharmaceuticals.

1. A centralized or
2. Decentralized or
3. Mutual Recognition

Centralized Procedure

1. Allows a pharmaceutical company to market its pharmaceutical products in all 25 member states.
2. Applicant can submit single application to EMEA for marketing authorization that is valid to all member state. (Applicant need not to obtain separate approvals for each member state). European drug approvals are overseen by the European Medicines Agency. The EMA is a decentralized body of the EU, with headquarters in London, England. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure). Marketing applications for drugs for use in humans ar evaluated by the Committee for Medicinal Products for Human Use (CHMP)
3. .Products that are eligible for review under the centralized procedure must meet the following criteria:
4. biologic drugs developed by recombinant technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods
5. medicinal products containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases
6. orphan medicinal products
7. Other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

2. Decentralized Procedure

1. Using the decentralized procedure, manufacturer can apply for simultaneous authorization in more than one EU country, that have not yet been authorized in any EU country and that do not fall the mandatory scope of the centralized procedure.
2. For products that fall outside the scope of the European Medicines Agency (EMA) with regard to centralized procedures, a sponsor can submit under the decentralized procedure. Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country.

3. Mutual Recognition Procedure

In mutual recognition procedure, a medicine is first authorized in one EU member state, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other EU countries in a procedure where by the countries concerned agree to recognize the validity of the original, national marketing authorization Mutual recognition procedure. With the mutual recognition procedure, a product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country.

CONCLUSION:

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. 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. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This work focuses on the drug approval process in India. Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article focuses on history, regulatory policy and administration, and related issues with respect to different countries like U.S.A. , Europe ,China, Australia and India.

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