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Review

Global process for generic drug approval

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Abstract

Drug approval standards in the United States are considered by many to be the most demanding in the world. Developing a new drug requires great amount of research work in discovery, development, preclinical research, clinical research. Reviewers in regulatory agencies throughout 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 work focuses on drug approval process in different countries like USA, Europe and India.

Keywords: API, FDA, INN

INTRODUCTION

Generic Drug

A generic drug is a pharmaceutical drug that contains the same chemical substance as a drug that was originally protected by chemical patents. Generic drugs are allowed for sale after the patents on the original drugs expire. Because the active chemical substance is the same, the medical profile of generics is believed to be equivalent in performance.[1,2] A generic drug has the same active pharmaceutical ingredient (API) as the original, but it may differ in some characteristics such as the manufacturing process, formulation, excipients, color, taste, and packaging.[2]

Although they may not be associated with a particular company, generic drugs are usually subject to government regulations in the countries in which they are dispensed. They are labeled with the name of the manufacturer and a generic non-proprietary name such as the United States Adopted Name (USAN) or International Nonproprietary Name (INN) of the drug. A generic drug must contain the same active ingredients as the original brand-name formulation. The U.S. Food and Drug Administration (FDA) requires generics to be identical to or within an acceptable bioequivalent range of their brand-name counterparts, with respect to pharmacokinetic and pharmacodynamic properties.[3] (The FDA's use of the word "identical" is a legal interpretation, not literal.)

Biopharmaceuticals, such as monoclonal antibodies, differ biologically from small-molecule drugs. Biosimilars have active pharmaceutical ingredients that are almost identical to the original product and are typically regulated under an extended set of rules, but they are not the same as generic drugs as the active ingredients are not the same as those of their reference products.[4]

In most cases, generic products become available after the patent protections afforded to the drug's original developer expire. Once generic drugs enter the market, competition often leads to substantially lower prices for both the original brand-name product and its generic equivalents. In most countries, patents give 20 years of protection. However, many countries and regions, such as the European Union and the United States,[5] may grant up to five years of additional protection ("patent term restoration") if manufacturers meet specific goals, such as conducting clinical trials for pediatric patients.[6]

Manufacturers, wholesalers, insurers, and drugstores can all increase prices at various stages of production and distribution.[7]

In 2014, according to an analysis by the Generic Pharmaceutical Association, generic drugs accounted for 88 percent of the 4.3 billion prescriptions filled in the United States.[8]

"Branded generics" on the other hand are defined by the FDA and National Health Service as "products that are (a) either novel dosage forms of off-patent products produced by a manufacturer that is not the originator of the molecule, or (b) a molecule copy of an off-patent product with a trade name."[9] Since the company making branded generics can spend little on research and development, it is able to spend on marketing alone, thus earning higher profits and driving costs down.[10] For example, the largest revenues of Ranbaxy, now owned by Sun Pharma, came from branded generics.[11,12]

Currently different countries have to follow different regulatory requirements for approval of new drug. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. Therefore it is necessary to have knowledge about regulatory requirement for MAA of each country.

Generic drugs are marketed after the expiries of the patent or marketing right of the patented drug are available at the affordable price. The generic drugs are approved by the respective controlling authority of the country as innovative drugs with regard to efficacy, bioavailability etc.Generic drugs may differ in shape, scoring configuration, release mechanisms, packaging, excipients (colors, flavors, preservatives), and product expiration. If drugs with such differences are substituted for each other, there is a potential for patient confusion. The main difference between generic and brand-name drugs is the amount and type of evidence supporting the market application of the respective drug. A brand-name drug is required to demonstrate substantial preclinical and clinical evidence showing safety and efficacy in a patient population. After the expiry of patent or marketing rights of the patented drug, generic drugs are marketed. Generic drugs are available at affordable prices with maintaining quality.The drug price competition and patent term restoration act of 1984, commonly known as hatch Waxman act allowed ANDA to be possible by making a comprise in drug companies. The hatch Waxman act of 1984 paved the way for the generic drug to enter to the market.with the increasing in pressure of healthcare costs all the large innovator companies as well as Indian MNCs drive up their business in generic market.[13,14,15] The pharmaceutical industry, while pursuing an international market, is obliged to comply with national regulations. The pharmaceutical industry is now perhaps the most highly regulated of all industries demanding a high level of information to be submitted to governments before a pharmaceutical product is brought to the market place. Regulatory authorities can be said to be the function responsible for obtaining and maintaining licenses to market medicinal products in as many countries as is necessary. According to the present laws all organizations involved in the development and marketing of medicinal products are legally required to have some form of regulatory support.[16] 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.[17] The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and wellbeing of the public.[18] There are few differences in the dossier submission requirements for among these five regions i.e. United State, European Union, India, Japan and Canada.[19] Thus a common format of submission will help in overcoming these challenges. Through the international conference on harmonization (ICH) process, common technical documents (CTD) for United State, European Union, India, Japan and Canada.[20]

Drug Company must submit an Abbreviated New Drug Application (ANDA) for approval to market a generic product. The drug price competition and patent restoration act of 1984 more commonly known as Hatch –Waxman Act (HWA), made ANDA possible by creating a compromise in drug industry. New drug's products are developed under patent protection. The patent protects the investment in the drug development by giving the company the sole of right to sell the drug while the patent is in effect. While the patent and other period of exclusively expire, manufacture s can apply to the FDA to sell generic version. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms are already are approved for safety and effectiveness. Health professionals and

consumers can be assured the FDA approved generic drug met the same rigid standard as the innovator drug.[21]

AIM AND OBJECTIVES

- To explore and compare the regulatory guidelines on generic medicines in various countries including India.
- The objective of generic drug policies is usually defined as reduction in expenditures without compromising health outcomes
- Submission of Clinical Trial application for evaluating safety and efficacy.
- Requirements for permission of new drugs approval.
- Post approval changes in biological products: quality, safety and efficacy documents.
- Preparation of the quality information for drug.
- Submission for new drug approval.

FDA approval, a generic drug must:

- Be identical in strength, dosage form, and route of administration.
- Have same use indication.
- Be containing the same active ingredient as the innovator drug.
- Bioequivalent
- Meet the same batch requirement for identity, strength, purity and quality
- Be manufactured under the same strict standards of FDA'S good practice regulation for innovator product.[22]

UNITED STATES

Drug approval standards in the United States are considered the most demanding in the world. The all new drugs must first be shown to be safe and effective before they can be approved by the Food nd Drug Administration (FDA) for marketing Discovering a new drug, FDA review process, can take many years, and cost hundreds of millions of dollars. To a large degree, these costs are mostly associated with the clinical testing that must be done to convince the agency that the new product is safe and effective for its intended medical use. To begin clinical testing, drug companies or sponsors must file an Investigational New Drug (IND) application with the FDA. The INDs must include information about the study protocol, the qualifications of the lead investigator, the trial's location, and assurance that the welfare of the study participants will be protected. Once new drug's clinical testing is complete, the sponsor submits a New Drug Application (NDA) for FDA evaluation. During the application's review, agency officials examine the drug's safety and efficacy data, assay samples, and conduct factory inspections to be sure the finished product will be manufactured properly . FDA also checks the drug's labeling to be sure that it is accurate and comprehensive. Once a new drug is approved, its safety is monitored through FDA's post-marketing surveillance.[23] Abbreviated New Drug Application(ANDA) contains data which when submitted to FDA Center for Drug Evaluation and Research, office of generic drug provides for the approval of a generic drug product. The legislation was created to balance the world of generic and brand drug industries. It provided accessibility to the cheaper generic drugs while still encouraging innovation and development of new drugs. The generic drug companies were allowed to market the drug after the patent and certain exclusivities expired. Hatch-Waxman amendment of the federal food, drug and cosmetics act established the process by which, would be marketers of generic drugs can file Abbreviated New Drug Application (ANDA) to seek FDA approval of generic drugs. Paragraph IV of the act, allows 180 day exclusivity to companies that are the "first-to-file" an ANDA against holders of patents for branded counterparts. In simple words "Hatch-Waxman act is the amendment to Federal, Food, Drug and Cosmetics act which established the modern system of approval of generics.[23]

Types of Applications

1. Investigational New Drug (IND)
2. New Drug Application (NDA)
3. Abbreviated New Drug Application (ANDA)
4. Biologic License Application (BLA)[24]

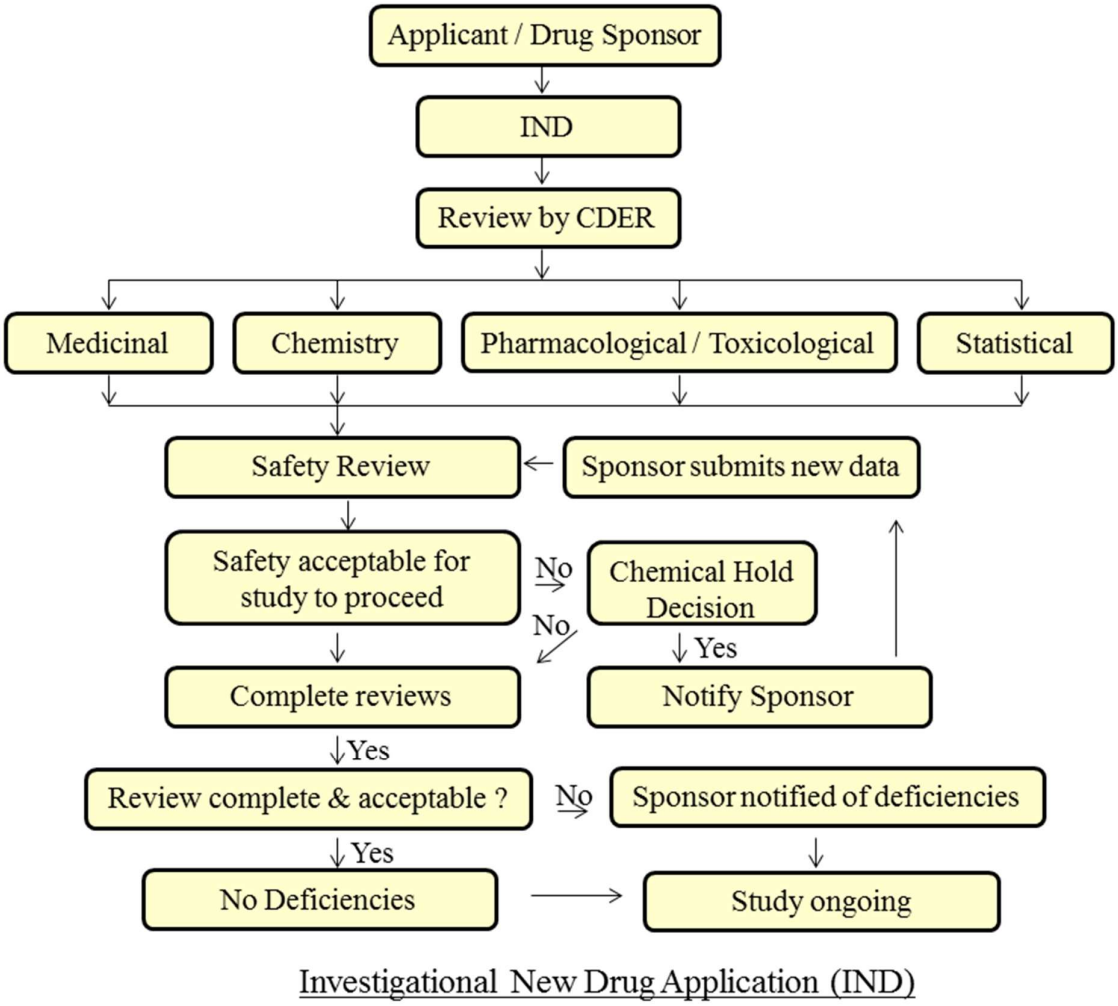

Fig 1: Flow chart of Investigational New Drug Application

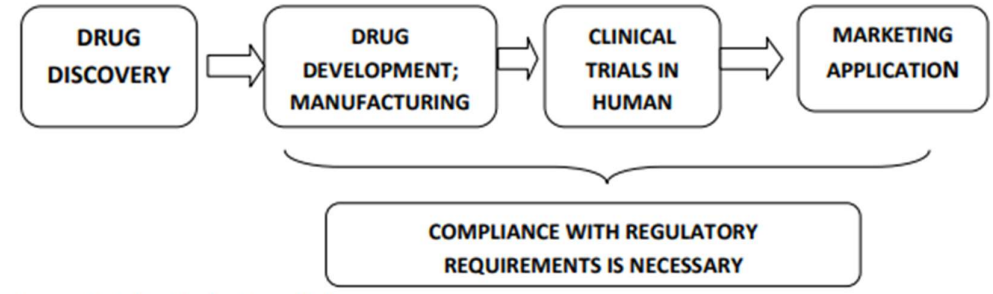

Fig 2: The Basic Regulation

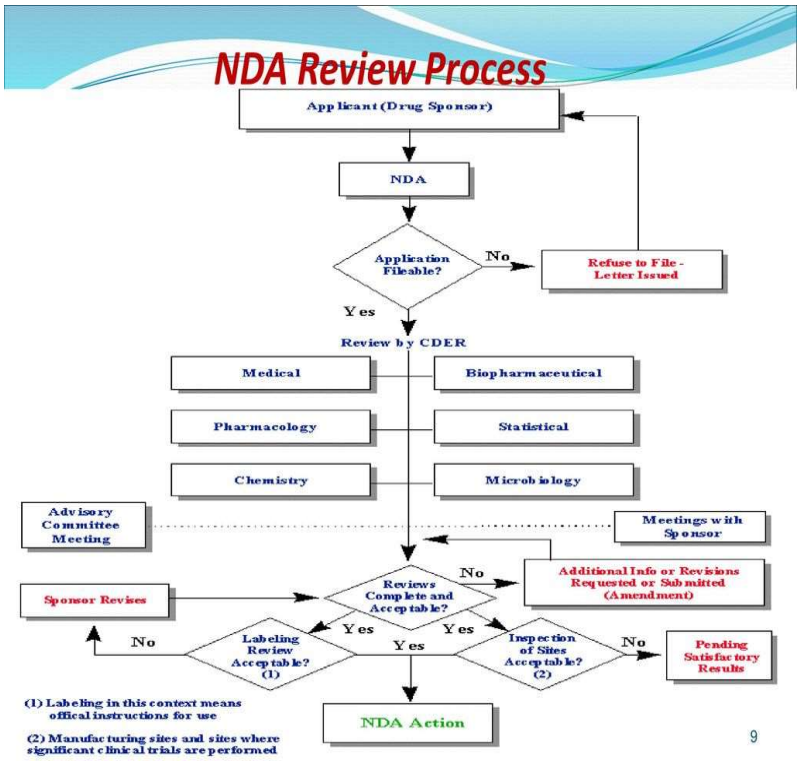

Fig 3: Flow chart of NDA

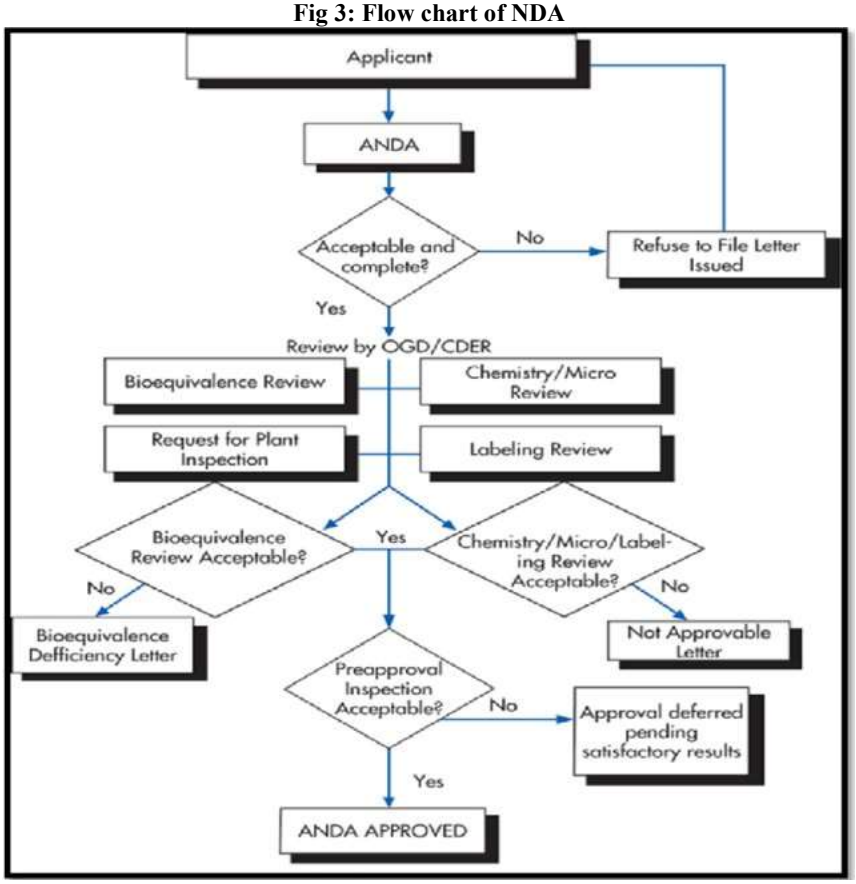

Fig 4: Flow chart of Abbreviated New Drug Application

GLP in Pharmaceutical Industry

Good Laboratory Practices (GLP) provide regulations and the standard by which drug safety studies are conducted in nonclinical animal studies. In addition to ensuring the ethical treatment and welfare of animals, adhering to GLP regulations gives sound evidence of the validity, integrity, and reliability of nonclinical safety data. This nonclinical safety data will ultimately be submitted to and evaluated by regulatory agencies for approval to use in clinical studies in humans.

GLP regulations have become an ingrained part of maintaining quality in drug development for many years, however these regulations are younger than one may think. The FDA issued the *Guidance for Industry Good Laboratory Practices Regulations* in 1978 in response to an observed lack of quality as well as scientific integrity in nonclinical toxicology studies in the mid-1970s.

The most notable instance being a scandal involving Industrial Bio-Test Laboratories in which former executives were accused of providing false data to chemical companies that were then submitted to the government to prove their products were safe.

Before the FDA implemented these regulations, New Zealand and Denmark released their own GLP regulations years earlier in 1972. The Organization for Economic Co-operation and Development (OECD) adopted these principles in 1992 to promote compliance on a larger scale. Both sets of regulations cover a vast array of sectors including:

- General provisions
- Organization and personnel
- Facilities and equipment
- Testing facilities operation
- Test and control animals
- Protocol for conduct of a nonclinical laboratory study
- Records and reports
- Disqualification of testing facilities

In the pharmaceutical industry, GLP regulations are the standard used to assure the quality and integrity of nonclinical drug safety studies conducted in animals. GLP regulations were first introduced by the FDA in 1978 and have become an integral part of nonclinical drug development. A key component of GLP is an independent quality assurance unit intended to monitor study conduct, analysis, and reporting of nonclinical studies.

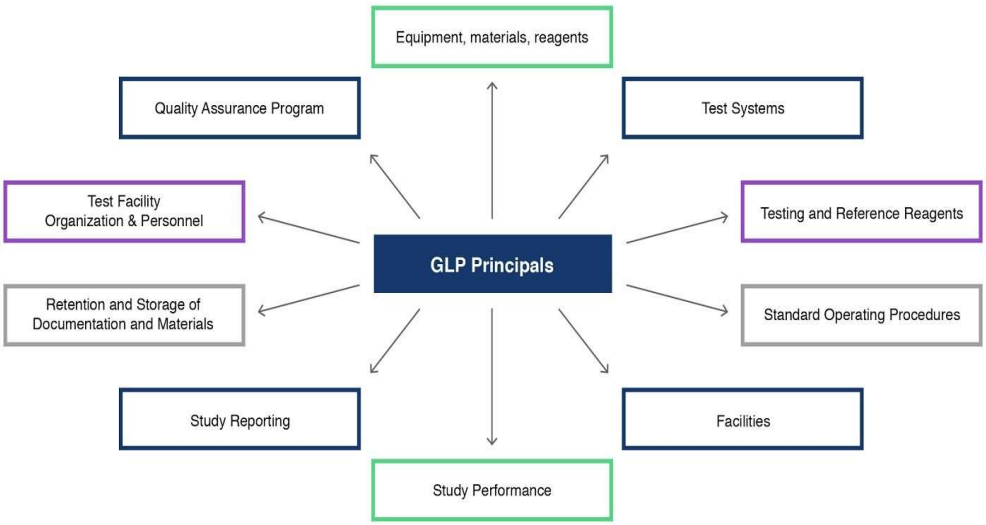

Fig 5 : Principles of GLP

Drug approval in Europe

Similar to the US requirements, there are two regulatory steps to go through before a drug is approved to be marketed in the European Union. These two steps are clinical trial application and marketing authorization application. There are 28 member states in the European Union (as of July, 2013); Clinical Trial Applications

are approved at the member state level, whereas marketing authorization applications are approved at both the member state and centralized levels. Centralized procedure The centralized procedure is one which allows applicants to obtain a marketing authorization that is valid throughout the EU.

- Results in a single authorization valid in EU, Norway, Iceland and Liechtenstein.
- Application evaluated by an assigned Rapporteur.
- Timeline: EMA opinion issued within 210 days, and submitted to European Commission for final approval.

Centralized process is compulsory for

- Those medicines which are derived from any biotechnology processes, such as genetic engineering.
- Those medicines which are intended for the treatment of Cancer, HIV/AIDS, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions.
- Medicines officially designated 'Orphan medicines' (medicines used for rare diseases). Mutual Recognition Procedure The Mutual Recognition procedure allows applicants to obtain a marketing authorization in the Concerned member states (CMS) other than the Reference member state (RMS), where the drug is previously approved.
- Applicant submits identical dossier to all EU member states in which they want marketing authorization, including required information.
- As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "RMS"), it notifies this decision to other Member States (which then become the "CMS"), to whom applications have also been submitted.
- RMS issues a report to other states on its own findings.
- Generic industry is the major user of this type of drug approval procedure. This process may consume a time period of 390 days. Nationalized Procedure The Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only.
- In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.

CONCLUSION

Drug approval or authorization process is one of the most regulated ones worldwide; in particular the developed nations such as the United States and the EU have the most stringent norms. That is expected because the primary purpose of regulations is to safeguard public health and ensure that the company's manufacturing and marketing pharmaceutical products complies with the regulatory norms. This calls for pharmaceutical products to be developed, formulated, produced, evaluated, and tracked conforming to the regulatory guidelines so that they are effective and safe and the patient's well-being is not affected. However this concern for safety and quality does not come cheap and that is why NDA process in a lot of developing countries remains less regulated. All clinical studies reports and related information regarding the approval of new drug in India should provide the necessary requirements along with the NDA to FDA. Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug.

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