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BRANDED/GENERIC DRUGS: GLOBAL ISSUES AND REGULATORY CONTROLS

T. Sukanya*, M. V. Nagabhushanam, Y. Ratna Sindhu, S. K. Sanjuda, R. Gnana Ramya, Brahmaiah Bonthagarala and G. Ramakrishna

Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

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***Corresponding Author**
T. Sukanya
Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

ABSTRACT

Different regulatory authorities regulate the drug development in various countries of the world. Various Regulatory authority for generic drug application Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceutical and Medical Devices Agency (PMDA), Health Product and Food Branch (HPFB) Central Drug Standard of Organization (CDSO). Generic manufacturers may file an abbreviated New Drug Application (ANDA) that incorporates the safety/effectiveness data submitted by original innovator drug manufacturer and adds only bioequivalence studies. Therefore it is very difficult and challenging task to approve a drug by the manufacturing companies, simultaneously submitted in all the regulatory authorities. Regulatory authorities are responsible to ensure the quality, safety, and efficacy including manufacturing, distribution of the drug product. There is lot of challenges for the pharmaceutical industry to development and filling of generic drug application, which can be overcoming by the common format of submission. This is due to the different regulatory procedure of the various countries. Through the international conference on harmonization (ICH) process common technical documents (CTD) has been developed for USA, EU, JAPAN, INDIA AND CANADA. There are few differences in the dossier submission for among these five regions. To development of any generic drug product still we need strategic planning by these regulatory authorities.

KEYWORDS: Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceutical and Medical Devices Agency (PMDA), Health Product and Food Branch

(HPFB), Central Drug Standard of Organization (CDSO), Abbreviated New Drug Application (ANDA), Common Technical Documents (CTD).

INTRODUCTION

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.[1] 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.[3] 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.[3] 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.[4] 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.[5] 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.[6] 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.[7] 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.[8] There are few differences in the dossier submission requirements for among these five regions i.e. United State, European Union, India, Japan and Canada.[9] Thus a common format of submission will help in overcoming these

challenges. Through the international conference on harmonization (ICH) process, common technicaldocuments (CTD) for United State, European Union, India, Japan and Canada.[10]

Introduction to generic drug

A generic drug is identical or equivalent to a brand drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drug are chemically identical to their branded counterparts, they are typically sold at substantial discount from the branded price.

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. 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.[11]

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 and 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.[12] 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 branddrug 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.[13]

Types of applications

1. Investigational New Drug (IND)
2. New Drug Application (NDA)
3. Abbreviated New Drug Application (ANDA)
4. Biologic License Application (BLA)[14]

Abbreviated new drug application review process

An applicant who su`bmits an abbreviated new drug application (ANDA) to obtain FDA approval to market generic drug product and any person whoowns an approved application or abbreviated application. Abbreviated new drug applications under 21 CFR subpart 314.94,

and amendments, supplements, and resubmissions; the items sent by parcel post or overnight courier service to the Office of Generic Drugs, should be directed to:

Office of Generic Drugs (HFD-600) Center for Drug Evaluation and ResearchFood and Drug Administration

Metro Park North II, Room 1507500 Standish Place

Rockville, MD 20855

Abbreviated new drug application

A generic drug product is one that is comparable to an innovator drug product (also known as the reference listed drug (RLD) product as identified in the FDA's ***list of Approved Drug Products with Therapeutic Equivalence Evaluations*** (orange book)in dosage form, strength, route of administration, quality, performance characteristics and intended use. Once approved an applicant may manufacture and market the generic drug product provided all patent protection and exclusivity associated with the RLD have expired. Generic drug applications are termed "abbreviated" in that they are not required to provide clinical data to establish safety and efficacy, since these parameters have already been established by the approval of the innovator drug product (first approved version of the drug product marketed under a brand name.[15]

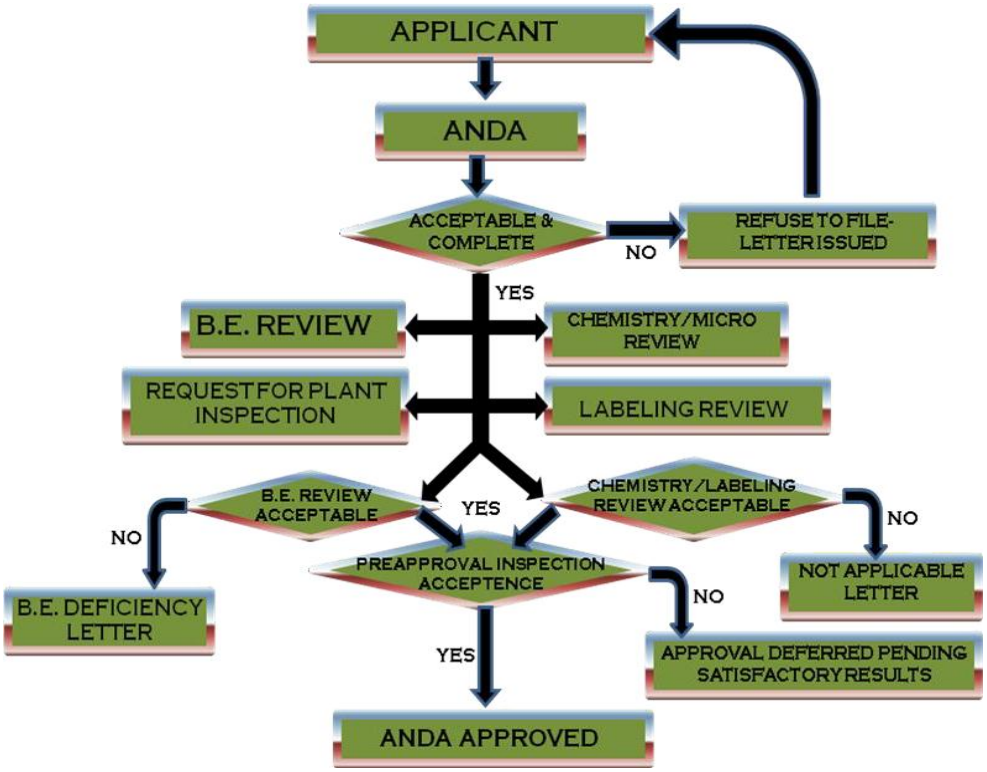

Fig. 1: ANDA review process.

General provision of hatch waxman act

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (the Act). The Hatch- Waxman Amendments created section 505(j) of the Act (21 U.S.C. 355(j)). Section 505(j) established the abbreviated new drug application (ANDA) approval process, which allows lower-priced generic versions of previously approved innovator drugs to be approved and brought on the market. Innovator drug applicants must include in a new drug application (NDA) information about patents that claim the drug product that is the subject of the NDA. FDA publishes this patent information as part of the *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is generally known as the *Orange Book.*

An ANDA applicant must include in the ANDA a patent certification described in section 505(j)(2)(A)(vii) of the Act. The certification must make one of the following statements:

- Para1) no patent information on the drug product that is the subject of the ANDA has been submitted to FDA;
- Para II) that such patent has expired;
- Para III) the date on which such patent expires; or
- Para IV) that such patent is invalid or will not be infringed by the[16]

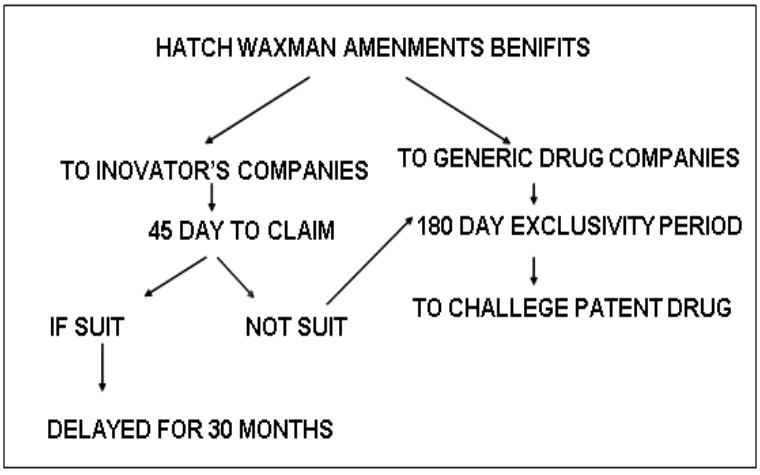

Fig. 2: Hatch waxman amendment.

Table 1: Comparison between NDA and ANDA.

NDA Requirement	ANDA Requirement
1. Labeling	1. Labeling
2. Pharmacology/toxicology	2. Pharmacology/toxicology
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls

6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal studies	9. Bioequivalence
10. Clinical studies	
11. Bioavailability	

Europe

The European Union (EU), consisting of 27 Member States, has continuously worked on improving and streamlining drug review and marketing authorization processes. There are currently three different procedures that can be used to submit a medicinal product for marketing approval in the European Union.

These three procedures are published by the European Commission in consultation with the competent authorities of the Member States, the European Medicines Agency (EMEA), and interestedparties. The three procedures that are:

1. Mutual Recognition Procedure (MRP)
2. Decentralized Procedure (DCP)
3. Centralized Procedure (CP)[17]

The European Medicines Agency is responsible for the scientific evaluation of applications for centralized marketing authorizations. Once granted by the European Commission, the centralized marketing authorization is valid in all EU and EEA- EFTA states (Iceland, Liechtenstein and Norway). This allows the marketing authorization holder to market the medicine and make it available to patients and healthcare professionals throughout the EEA.[18]

According to Article 10(1) of Directive 2001/83/EC a generic application can also be submitted in a Member State where the reference medicinal product has never been authorized.

Directive 2001/83/EC defines a generic medicinal product in Article 10(2) (b) as a medicinal product which has:

- The same qualitative and quantitative composition in active substances as the reference product.
- The same pharmaceutical form as thereference medicinal product.
- And whose bioequivalence with the reference medicinal product has been demonstrated

by appropriate bioavailability studies.[19]

Table 3: Marketing authorization procedure in EU.

Regulatory agencies	Procedure	Function of regulatory agencies
EMA	Centralized procedure	Applications for the centralized procedure are madedirectly to the European Medicines Agency (EMA) and lead to the granting of a European marketing authorizationby the Commission which is binding in all Member States.
Reference memberstate	Decentralized procedure(DCP)	Through this procedure an application for the marketing authorization of a medicinal product is submitted simultaneously in several Member States, one of thembeing chosen as the "Reference Member State". At the endof the procedure national marketing authorizations are granted in the reference and in the concerned Member States.
Reference memberstate	Mutual Recognition procedure (MRP)	The mutual recognition procedure, which is applicable to the majority of conventional medicinal products, is based on the principle of recognition of an already existing national marketing authorization by one or more Member States.
Member state	National procedure	National authorizations are still available for medicinalproducts to be marketed in one Member State only.

India

Drugs are regulated in India both central and state level through the CDSCO (Central drugs standard control organization) under the ministry of health and family welfare are responsible for approval new drugs, clinical trials and licensing of drugs. Drug regulatory authorities issue the licenses at the state level. The regulation of drugs, medical devices and biological products in India is distributed with in various ministries.[20]

There are mainly two regulatory bodies which regulate the drug approval, marketing, production,quality and drug price in India.

CDSCO (The Central Drug Standards and Control Organization)

Ministry of Health and Family Welfare control the function of CDSCO

CDSCO evaluate the standards and measures for ensuring the safety, efficacy, and quality of drugs andcosmetics.

CDSCO also regulates the market authorization of new drugs and standards of clinical trials.

CDSCO controls drug imports and approves licenses to manufacture the above-mentioned products.

NPPA (The National Pharmaceutical Pricing Authority)

Department of Chemicals and Petrochemicals controlthe function of NPPA.

NPPA fixes or revises the price of bulk drugs and formulations.

NNPA updates the list under price control through inclusion and exclusion of drugs in line with prescribed guidelines.

NPPA also maintains data on production, exports and imports and market share of pharmaceutical firms.

NPPA monitors the shortage of medicines in addition to providing inputs to Parliament in issues pertaining to drug pricing.[21]

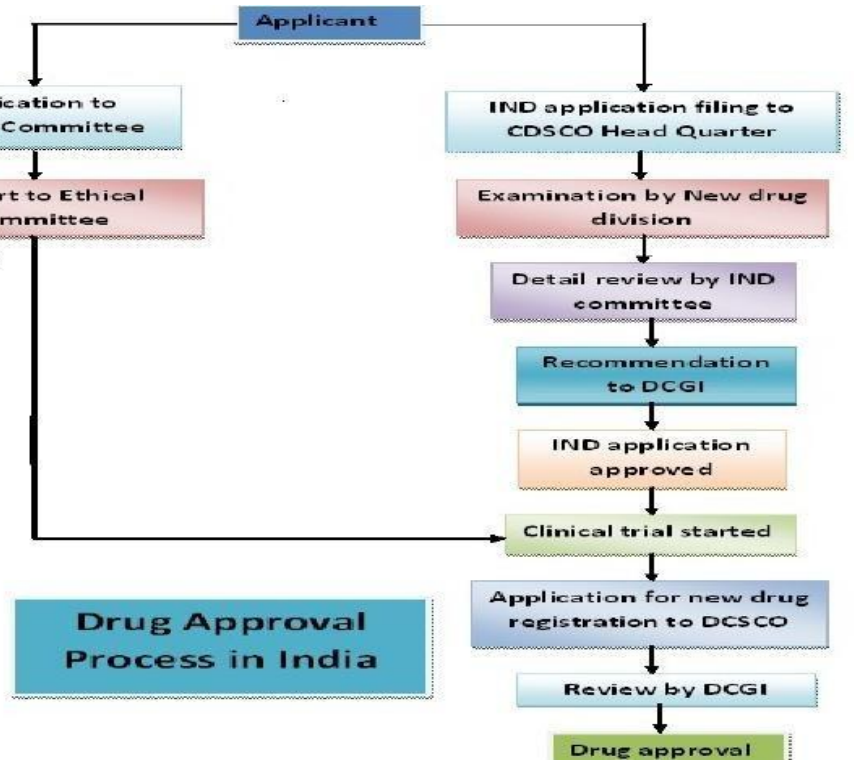

Fig. 3: Generic drug approval process in INDIA.[12]

1. Generic drug require Form 44 for approval in India.
2. A treasury challan of INR 15,000 is required all the active ingredients for more than one year and INR50,000 of the active ingredients is approved for less than one year in India.

3. Manufacturing of bulk drugs and raw materials the applicant has a manufacturing license for bulk drugs, a copy of the same is needs to be submitted.
4. Chemical and pharmaceutical information including:

Information on active ingredients

a) Brief Chemical & pharmaceutical data on Formulation
b) Master manufacturing formula
c) Details of the formulation (including inactive ingredients)
d) Finished product specification
e) In process quality control check
f) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.
g) Comparative Dissolution data in case oral dosage form as appropriate
h) Stability study evaluation as per requirements of schedule Y

1. Regulatory status of the drug including names of the company's marketing the drug in the country
2. Bioavailability/Bioequivalence study reports (for oral dosage forms
3. In case of injectables formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.
4. Prescribing information
5. Draft of labels and carton
6. Copy of License in Form-29[22]

The Indian generic drug Pharmaceutical Industry is the top five producers of bulk drugs in the world. The Pharmaceuticals market can be divided into Bulk drugs and formulations. The bulk drug acquire 20% of the market with growth rates of 20% and formulations acquire 80% of the market with an annual growth rate of 15%.The Indian generic drug market growing rapidly because a lot of patent expire, major pharmaceutical companies of the world interested to invest in Indian market.[23]

Japan

Generic drug approval review in Japan is conducted by the Office of Generic Drugs.[24] which is part of the Pharmaceuticals and Medical Devices Agency (PMDA), is responsible for the approval review of generic drugs in Japan. The PMDA reviews the equivalence of generic and original drugs from the viewpoint of quality, efficacy, and safety, based on a document

submitted by generic drug applicants. There are two application types for new generic drugs and partial change approval in Japan. New generic drug applications are submitted as the first application, and partial change applications are submitted after for post-approval changes. The approval content in Japan includes the indication, effects, directions, dose, specifications, test methods, storage method, validity period, manufacturing method, formulation or manufacturing site, and brand name. If the applicant for a generic drug performs post-approval change on these contents, with the exception of minor changes, the PMDA review is necessary for partial change approval.[25]

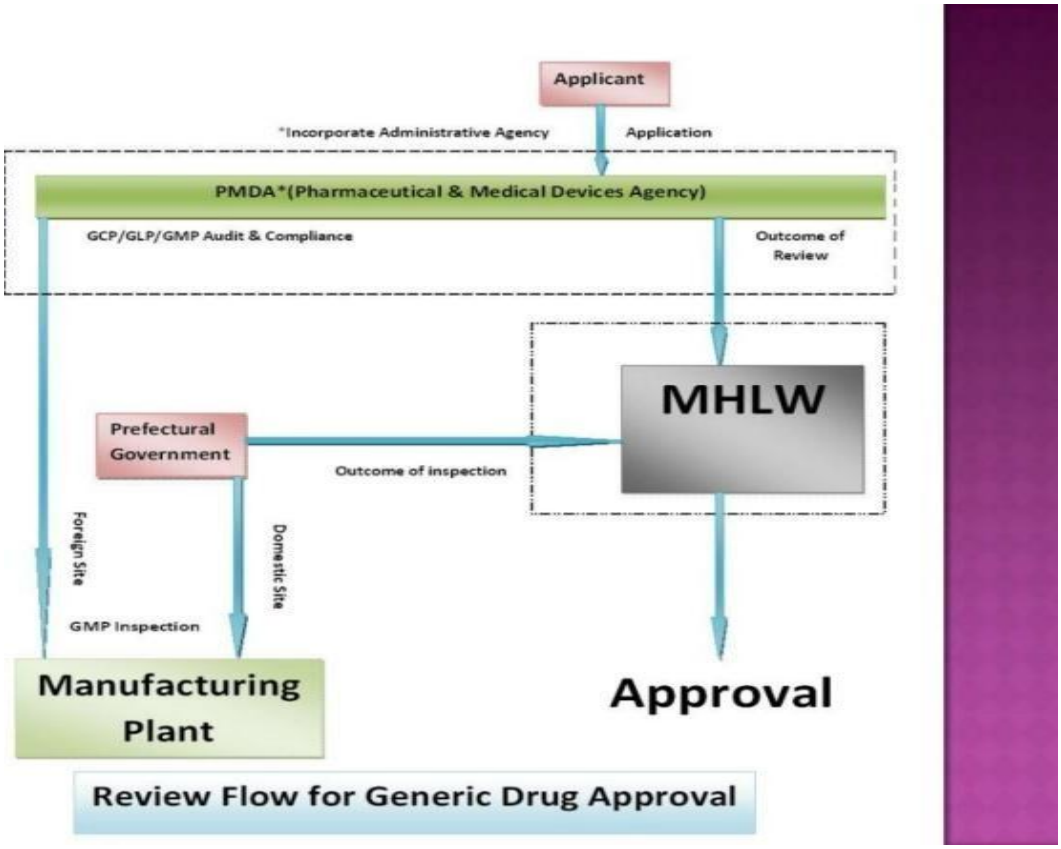

Fig. 4: Generic drug approval process in Japan.

Main data required for the approval of generic drugs

a) The manufacturing methods, standards, and test methods, which are used for evaluations of specificationsand test methods (and manufacturing methods, in some cases).

b) Stability data, which is used to conduct accelerated tests.

c) Absorption, distribution, metabolism, and excretion data, which are used in bioequivalence evaluations.[26]

Table 4: Data required for the approval of generic drugs.

Requirements in Japan (Data to be submitted with an application for approval)		Originator Data required	Generic Data require
A. Origin or background	1) Origin or background of discovery	Yes	No
	2) Condition of use in foreign country	Yes	No
	3) Special characteristics, comparisons with other drugs etc.	Yes	No
B. Manufacturing methods,standards and test methods	1) Chemical structure and physiochemical properties etc.	Yes	No
	2) Manufacturing methods	Yes	Case based
	3) Specification and test methods	Yes	No
C. Stability	1) Long term storage test	Yes	No
	2) Test under service conditions	Yes	No
	3) Accelerated tests	Yes	No
D. Pharmacological action	1) Test to support efficacy	Yes	No
	2) Secondary pharmacology, safety pharmacology	Yes	No
	3) Other pharmacology	Yes	No
E. Absorption,distribution, metabolism and excretion	1) Absorption	Yes	No
	2) Distribution	Yes	No
	3) Metabolism	Yes	No
	4) Excretion	Yes	No
	5) Bioequivalence	Yes	No
	6) Other pharmacokinetics	Yes	No
F. Acute sub-acute and chronictoxicity, teratogenicity and other toxicity	1) Single dose toxicity	Yes	No
	2) Repeated dose toxicity	Yes	No
	3) Genotoxicity	Yes	No
	4) Carcinogenicity	Yes	No
	5) Reproductive toxicity	Yes	No
	6) Local irritation	Yes	No
	7) Other toxicity	Yes	No
G. Clinical study	Clinical trial results	Yes	No

Generic drug market share in Japan

The share of generics in the prescription drugs market has been dramatically increasing in terms of both volume and value. The recent volume share was 60.1% in the 2nd quarter in 2016.[27]

Japanese government introduced an initiative for increasing generic usage that aims to increase genericshare by volume to over 60 percent by the end of FY2017 (March 2018).[28]

Japan represents the world's eighth biggest market for generic drugs. The government has also made a target towards achieving a generic penetration of 60% by 2017. This is expected to create huge opportunities for both domestic and foreign generic manufacturers in Japan.[29]

Canada

Generic pharmaceuticals generics play an important part in helping to control prescription drug costs in Canada. Generics are determined by Health Canada to be "bioequivalent" to patented pharmaceuticals. Their role is to provide competition for brand name products when their patent protection ends. In order to market an IG in Canada, a manufacturer must obtain approval from Health Canada under the Patented Medicines (Notice of Compliance) Regulations (NOC Regulations).[30]

All drugs sold in Canada (including pharmaceuticals, natural health products, biological and radiopharmaceuticals) – both those manufactured domestically and imported, must be authorized for sale by Health Canada.

New Drug Submissions and Supplementary New Drug Submissions (SNDS)

To gain Health Canada authorization for a new drug, a manufacturer, typically an innovator, submits a New Drug Submission NDS setting out all data (obtained through rigorous clinical testing) establishing the safety and efficacy of the drug. Such submissions typically require pre-clinical, clinical, chemistry and manufacturing data. Health Canada then reviews the submitted information and evaluates the drug's safety, efficacy and quality to determine whether it is suitable to be marketed in Canada and whether a Notice of Compliance should, accordingly, be issued. Once a drug has been approved, any changes to the approval (e.g., change of name, packaging, product monograph) requires the manufacturer to file a Supplementary New Drug Submission SNDS. Changes requiring the submission of a SNDS are those made:

i. In the identifying name of the drug product or the brand name;
ii. In the dosage form or strength of the drug product;
iii. In the formulation, method of manufacture, equipment, or process control of the drug product that requires supporting clinical or bioequivalence data;
iv. In the case of Schedule C and D drugs, in the production site, method of manufacture, equipment and process control of the drug substance or in the formulation, method of manufacture, equipment, process control or production site of the drug product;
v. In the labeling, including package inserts, product brochures, file cards, and product

monographs of the drug product respecting, either explicitly or implicitly:

a) The recommended route of administration ofthe drug product;
b) The dosage of the drug product, and
c) The claims, including indications, made for the drug product; or for sterile drug products, in the specifications to remove the sterility test and replace it with process parametric release.

Abbreviated New Drug Submissions (ANDS)

Where a second or subsequent manufacturer, typically a generic manufacturer, seeks a Notice of Compliance on the basis of a direct or indirect comparison between its drug and the original innovative drug which has already received marketing approval (called the "Canadian Reference Product"), the generic manufacturer submits an Abbreviated New Drug Submission (ANDS) demonstrating that the generic formulation of the drug is bioequivalent to the brand formulation. The ANDS typically does not contain clinical data. By establishing bioequivalence, a generic manufacturer may demonstrate the safety and effectiveness of its drug by comparison, without having to complete costly and time-consuming clinical trials.[30]

Comparison of generic drug filling in different countries

worldwide Food and Drug Administration (FDA) in United States, European Medicine Agency (EU) in Europe, Central Drug Standard Control Organization (CDSO) in India, Ministry of Health Labor The regulatory requirements and filling procedure of drug product of different countries in the world are different from each other. The role of these regulatory authorities is to ensure the quality, safety, and efficacy of all medicines in their country. The pharmaceutical industry is one of the highly regulated with many rule and regulation enforcement by the government to protect public health. It is the responsibility of the national government to establish regulatory with strong guidelines for quality assurance and drug regulation in the different territories. The aim of the pharmaceutical industry is to identify and develop a generic drug product. To make a generic drug product formulator, must know the details of the exact regulatory requirements and filling procedure of each concerned countries. Generic drug development uses a different approach and strategy compared to that used to develop a innovator drug product. Generic drug manufactures must formulate a drug product that will have the same therapeutic, safety and performance characteristics as of brand name product. Different regulatory authorities which are use as and Welfare (MHLW), Health Product and Food Branch (HPFB) in Canada, Medicines and Healthcare Products

Regulatory Agency (MHRA) In UK, Therapeutic Good Administration (TGA) in Australia.

Comparison Table 5:

Sr no.	Requirement	Us	Eu	India	Japan	Canada
A. Administrattion						
1	Regulatory authority	Food and drug administration	European medicine agency	Central drug standard and control organization	Ministry of health labor and welfare	Healh product and food branch
2	Application	Anda	Maa	Maa	Pdma	Ands
3	Debarment certification	Required	Na	Na	Na	Na
4	No. Of copies	3(archival, Review, field)	1	1	Not specified	3
5	Approval time line	18 month	12 month	12 month	12 months	12-18 Month
6	Clinical studies fees		10-20 lakh	50000 rs.	654200 yen	10000$
7	Presentation	Ectd & paper	Ectd, Paper along with nees	Paper	Ectd	Ectd
8	Pharmacovigilance	Not required	Required	Required	Required	Required
9	Agent authorization	Required	Not required	Not required	Not required	Not Required
B. Finished product control						
1	Assay	90-100%	95-105%	90-110%	90-111%	90-110%
2	Disintegration	Not required	Required	Required	Required	Required
3	Colour identification	Not required	Required	Required	Required	Required
4	Water content	Required	Not required	Required	Required	Required when material Hygroscopic
C. Manufacturing and control						
1	No. Of batches	1	3	1	1	3
2	Packaging	A Minimum of 100000 Unit	Not required	Notsuch required	Not such required	100000 Unit
3	Process validation	Not required at the time of Submission	Required	Required	Required	Required
D. Labeling requirement						
1	Prescription status	Rx	Pom	Rx	Rx	Rx
2	Labels	Vials/carton/pil	Vials/carton/pil	Proposed draft labels and cartoons Provided in	Vials, ampoules,injections	Blister pack, bottle, cover, sachet, strip Pack, tube,

				module 1		vessel, vial
3	Side by side comparison	Required	Required	Required	Not specified	Required
E. STABILITY						
1	Date and submission	time	of	3months accelerate and3 months long term	6 months accelerate and6 months long term	6months accelerate and 3months longterm
2	Container orientation	Inverted upright	Do address	not	Do not address	Don not address
3	QP certification	Not required	Required	Required	Required	Required
5	Retention of sample	5 years from the date of filing the application	No required usually followed	suchbut	3 years from the date of filing the application	Not such required

SUMMARY AND CONCLUSION

Generic drug manufacturing is a major part of the pharmaceutical industry and grow rapidly because to the patent expire of the branded drugs. The strategy of encouraging generic drug production is important at a global level to reduce healthcare costs and to enhance drug availability to patients. Generic manufacturers may file an abbreviated New Drug Application (ANDA) that incorporates the safety/effectiveness data submitted by original innovator drug manufacturer and adds only bioequivalence studies. Paragraph IV provides a mechanism for the litigation of patent infringement disputes. Hatch-Waxman Act has generally achieved the dual goal availability of cheap drugs to consumer and providing incentives to innovator pharmaceutical drug manufacturers to continue producing innovative drugs. Hatch-Waxman established a regulatory framework to balance, to entry of generic drugs by providing incentives to brand name companies.

In the present study, an attempt was made to search the current status of generic drug in global market and their regulatory environment. I have studied five different countries US, Europe, Japan India and Canada although there is a continuous process of harmonization.

It is concluded that United Sates have the toughest drug approval standard in the world. To sold a new a drug the pharma manufacturer have to give the proof of safety and effectiveness of drug required by the law.

In EU pharmaceutical industries follow three approval procedures Centralize, Decentralize

and Mutual Recognition Procedure. For the approval of generic drug product Decentralize Procedure is followed and in case of new drug approval application of marketing authorization is always submitted through centralize procedure. The EMEA is getting global attention and become gold standard in global pharmaceutical.

The Central Drugs Standard Control Organization (CDSCO) is the major medical regulatory organization in India. Now a day the generic pharmaceutical market is an attractive market for Indian pharmaceutical companies due to highly qualified pool of chemist and low-cost environment. It is studied that the condition for approval of generic drug is not so easy than EU and US.

In Japan the approval process for generic drug is modernizing and government of Japan has ambitious goal for improvement of generic drug. Japan has the world largest medical market and this country is the major target for foreign innovator companies.

Canada has one of the world's largest pharmaceutical market. Although it has a share of only 3% in the global market. Canadian pharmaceutical market and the four elements making it unique including (i) the historical compulsory licensing regime (ii) the division of customers by federal, provincial and territorial drug plants, (iii) the influence of two to three large pharmaceutical chains with limited advertising due to self-imposed restrictions and (iv) the principal agent problem.

It was studied that most regulated authorities are similar but a small degree of different requirement for the approval of dosage form. It is also concluded that similar studies may be performed repeatedly to fulfill regulatory environment in different regions of the world. The need of standardize regulatory requirement has been approved by both regulatory authorities and pharmaceutical industry.

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