

Comparison of Generic Drug Application and their Approval Process in US, Europe and Japan

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Abstract:

Abbreviated new drug application (ANDA) can be filed to the regulatory authorities, to get generic drug approval. Under section 505(j) of Hatch-Waxman act, an abbreviated new drug application may be filed for any generic versions of the reference listed drug. This study was conducted with an objective to compare the regulatory framework of generic drug application and their approval process in various countries like USA, EUROPE, and JAPAN. This study mainly emphasizes on the application form, approval timelines and sequence of steps in the generic drug approval.

Key Words: Generic drug, ANDA, Regulatory Requirements, Approval Process, USFDA, EMA, PMDA.

INTRODUCTION:-

ABBREVIATED NEW DRUG APPLICATION

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Centre for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD), provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. In other words, "It is an application which is filed with USFDA for generic drug approval of an existing licensed medication or approved drug."^[1]

GOALS OF ANDA

- To reduce the price of the drug.
- To reduce the time of drug development.
- To increase the bioavailability of the drug in comparison to the reference listed drug product.

GENERIC DRUG PRODUCT

USA defines a generic drug product as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use".^[2]

The EMA defines a generic medicine as "a medicine that is developed to be the same as a medicine that has already been authorised" (the 'reference medicine').

A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s) as the reference medicine. However, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine.^[3]

The Japan defines a generic medicine as "a drug with the same active pharmaceutical ingredient (API), dosage form, strength, quality, indication, effect, direction, and dose as the original proprietary drug".

FACTS ABOUT GENERICS AND GENERIC DRUG APPLICATIONS (ANDA)

- 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.

- Generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug).
- Bioequivalence is generally determined by measuring the time taken for generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives the rate of absorption, or bioavailability, of the generic drug, which can be compared 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.
- 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 "*Hatch - Waxman Act*".

HATCH WAXMANN ACT

It is the popular name for Drug Price Competition and Patent Term Restoration Act, 1984. It is considered as the landmark legislation which established the modern system of generic drugs in USA. Hatch-Waxman act is the amendment to Federal, Food, Drug and Cosmetics act which established the modern system of approval of generics through Abbreviated New Drug Applications (ANDAs). 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.

SIGNIFICANT RESULTS DUE TO HATCH-WAXMAN ACT

- Prior to the Hatch and Waxman act the generic drug manufacturer had to do the entire clinical trials. After the passage of Hatch and Waxman act the generic drug manufacturer had to only prove bioequivalence of generic drug to the innovator drug by showing that the generic drug is 80-125% bioequivalent to the innovator drug.
- The time and cost involved for getting the generic drug into the market was significantly reduced.
- Low cost quality, safe and effective generic drugs were available to the patients.
- Since 1984, over 10,000 generic drugs have entered the market, and generics accounted for close to 50 percent of

prescriptions filled (as on august 1, 2003) Billions of dollars in health care costs are being saved annually.

TYPES OF PATENT CERTIFICATIONS

As per the Hatch Waxman act, generic drug applicants should include certifications in their applications for each patent listed in the “Orange Book” for the innovator drug. This certification must state one of the following:

TYPE	PATENT CERTIFICATION	ANDA FILING
Paragraph I	The drug has not been patented.	If a generic drug manufacturer certifies I & II, then the FDA starts processing the generic ANDA right away
Paragraph II	The patent has already expired.	
Paragraph III	The generic drug will not go on the market until the day of expiry of the patent	If a generic drug manufacturer certifies 3, then the FDA starts processing the ANDA, and gives approval when the patent expires
Paragraph IV	The patent is not infringed or is invalid	ANDA filer notifies patent holder within 20 days – Patent holder must sue for infringement within 45 days – If the patent holder sues, FDA must withhold approval for 30 months (one time only) – If the patent holder does not sue, FDA may approve ANDA at any time – If a court rules that the patent is not infringed or invalid, FDA may proceed after decision. – If first generic ANDA files will get 180 days exclusivity (per product)

OVERVIEW OF USA GENERIC MARKET

The US generic drugs market accounts for a share of around 45% in the global Generics market. This share has been growing at a fast pace on the back of factors, such as demand for cost-effective medications, rising healthcare expenditure, increasing ageing population, patent expiration of blockbuster drugs, and enhanced government support.

According to RNCOS "US Generic Drug Market Outlook 2018", the US Generics market, which was US\$ 43.5 Billion in 2013, is anticipated to grow at a CAGR of around 11% during 2013-2018. [4]

REQUIREMENTS FOR ANDA FILING IN USA

- SIGNED FDA FORM 356h**, which provides information regarding the applicants name and address, name of the drug product, the product strength & route of administration, indication of drug master files cited, proposed indications, a statement regarding whether the product is for the prescription over counter.
- An **index** should specify volume and page number of each complete and detailed item.
- Information on the basis for which the ANDA is being submitted**
 - Name of the reference drug, its dosage form and strength.
 - Information on exclusivity for the listed drug.
 - If a suitability petition is approved a reference to the FDA number that was assigned to the suitability petition.
- Condition for use**, including,
 - A statement regarding the condition for which the drug will be used.
 - A reference to the annotated labelling for the product and the currently approved labelling for listed drug product

5. A statement that an **active ingredient** is the same as for that of the reference drug. For the combination product this must be shown for both active ingredients.

6. **Route of administration, dosage form and strength**, this should include a statement that the route of administration, dosage form and strength are same as the reference drug

7. **Bioequivalence** this should include information to demonstrate that the proposed drug is bioequivalent to the reference listed drug product.

8. **Labelling**, a copy of currently approved labelling for the listed drug as well as the proposed labelling for the drug being provided for in ANDA. A side by side comparison of two sets of labelling is also necessary.

9. **Chemistry, manufacturing and control**, describe the composition, manufacture, specifications and analytical procedures for the drug substance and drug product

10. **Human pharmacokinetics and bioavailability:** This includes information concerning

- The design
- The dosing procedure

11. **Samples:** The samples of the drug substance and finished product should be provided four individual units with sufficient quantities in each unit to permit the FDA to perform all the tests included in the specifications at least three times.

12. **Analytical method for drug substance and drug product:** This specification should consist of the specifications, analytical methods certificates of analysis, method of analysis, method validation and stability indicating data as contained in the chemistry, manufacturing and control part of the application

13. Labelling:

Twelve specimen of the final printed label and all labelling for the drug product should be included.

Case report forms and tabulations: The need for these should be discussed with the appropriate personnel of the division of bioequivalence prior to submission of the ANDA. [5]

ABBREVIATED NEW DRUG APPROVAL PROCESS IN USA

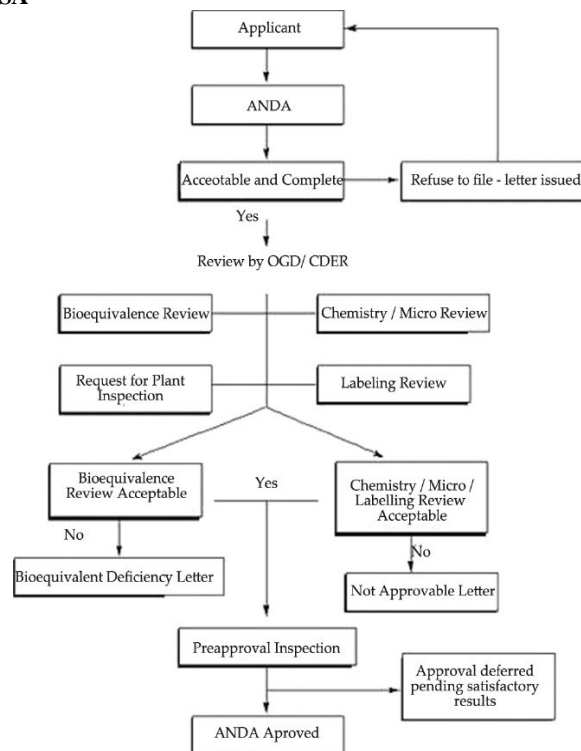


Figure-1 ANDA APPROVAL PROCESS IN USA

OVERVIEW OF EUROPEAN GENERIC MARKET

In most European countries, the market share of generic medicines by volume is more than 40%, Germany, which is the biggest pharmaceutical market in Europe, had the highest volume share of generics of 73% in 2014.

Generics make a major contribution to the European drug supply, according to a report by the by Germany-based Institute for Healthcare and Social Research (IGES).^[6]

GENERIC DRUG APPROVAL PROCESS IN EUROPE

In Europe, the drugs are marketed only after the marketing authorization approval. European generic medicines are approved through 4 marketing authorisation procedures namely,

1. Centralised procedure.
2. Mutual-recognition procedure.
3. National procedure.
4. Decentralised procedure.

CENTRALISED PROCEDURE

- In centralised procedure with one application Eu-wide marketing authorisation will be issued by the European commission, a legal authority that grants marketing authorisation.
- The centralised procedure laid down in Regulation 724/2004 and Directive 2004/27/EC.
- Applications are made directly to the EMA and lead to a grant of a European marketing authorization by the EU Commission within 7 months after application (210 days).
- One Member State is assigned Rapporteur for an application and takes the lead in the evaluation process of the CHMP.
- The decision of the Commission is binding on all EU Member States. The product may be marketed in all Member States with one common Summary of Product Characteristics (SPC).^[7]

MANDATORY FOR THE CENTRALISED PROCEDURE

- Biotechnological medicinal products,
- Orphan medicinal products
- New active substances for which the therapeutic indication is the treatment of Diabetes, Cancer, Acquired immune deficiency syndrome, Neuro-degenerative disorder, Auto-immune diseases and other immune dysfunctions – Viral diseases

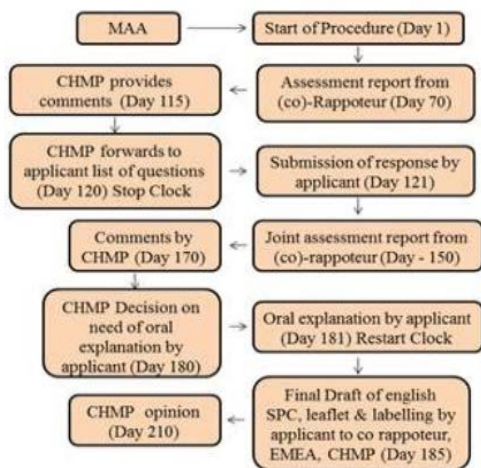


Figure-2 CENTRALISED PROCEDURE

Optional for the Centralised Procedure:-

- New active substances
- Innovative medicinal products

MUTUAL-RECOGNITION PROCEDURE

- The Mutual Recognition Procedure is stated in Council Directive 93/39/EEC.
- In essence, once a drug is approved for marketing authorization by one Member State, it is eligible to apply for marketing authorization in other Member States through the mutual recognition procedure in place since 1998.
- Identical applications are submitted to those Member States where marketing authorizations are sought.
- The first Member State that reviews the application is called the 'Reference Member State'. It notifies other states, called 'Concerned Member States'.
- Concerned Member States may suspend their own evaluations to await assessment by the Reference Member State.
- The decision of the Reference Member State is forwarded to the Concerned Member States.
- If the Concerned Member States reject mutual recognition, the matter is referred to the CHMP of the EMA for arbitration.
- The EMA forwards its opinion to the European Commission, which makes the final decision. Altogether, the decision process may take up to 300 days if there is no objection, and 600 days when objections are raised.

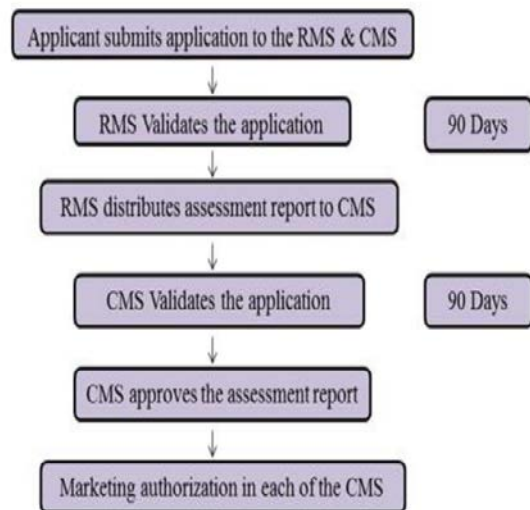


Figure-3 MUTUAL RECOGNITION PROCEDURE

NATIONAL PROCEDURE:-

- This procedure is used whenever a company wants to commercialize a product in only one EU Member State
- The National procedure is specific to each country. That is, each country within the EU has its own procedures for authorizing a marketing application for a new drug.
- Sponsors can find information regarding the requirements and procedure of each country on the websites of the regulatory agencies.
- To obtain marketing authorization in a country, the application must be submitted to the Competent Authority of that Member State in its own language.

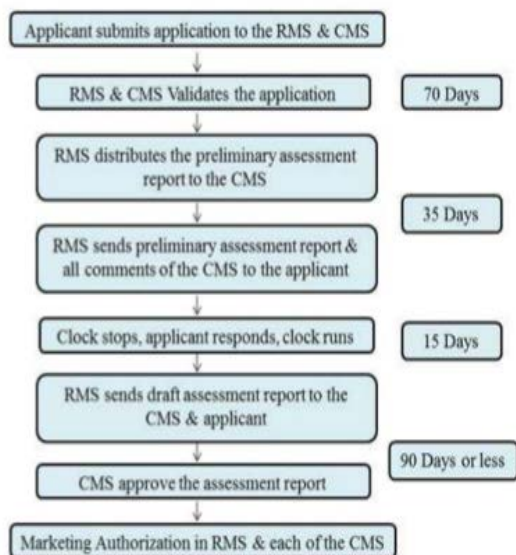


Figure-4 DECENTRALISED PROCEDURE

DECENTRALISED PROCEDURE

- The objective of this procedure is to obtain marketing authorizations in several Member States, when no marketing authorization has been granted in the European Community.
- The applicant should send an application to the competent authorities of each of the Member States, where there is intent to obtain a marketing authorization.
- The applicant may designate a country to act as the Reference Member State (RMS).
- The RMS will start the procedure after the application is determined to be complete by both the RMS and all the CMS(s).
- The RMS forwards a preliminary Assessment Report on the dossier to the CMS(s) and the applicant within 70 days.
- The CMS(s) is asked to give comments on the proposed national prescription status and to inform the RMS.
- On day 105, the RMS will forward all comments to the applicant and stops the clock if necessary, until the applicant prepares a response document.
- The RMS prepares a Draft Assessment Report on day 120 and may close the procedure if a consensus has been reached between the CMS(s) and the RMS.
- Otherwise, the CMS(s) has 90 more days to approve the Draft Assessment Report, and other documents.

- Competent authorities of the RMS and the CMS(s) adopt a decision within 30 days after acknowledgement of their agreement to the Assessment Report and other documents. ^[9]
- At the end of the Decentralized Procedure with a positive agreement, a national marketing authorization will be issued in the RMS and each of the CMS(s).

KEY ADVANTAGES OF DECENTRALISED PROCEDURE STRONG COMMERCIAL ADVANTAGE

The applicant receives identical marketing authorisation for its medicinal product in all chosen member states at the same time, it is possible to launch a product on the market in several different EU countries simultaneously, thus reducing the associated launch costs and potentially creating a strong band and presence for the product in the EU from day one. ^[10]

OVERVIEW OF GENERIC MARKET IN JAPAN

The generic drug penetration in the country is expected to reach 60% in fiscal 2017, followed by 70% in fiscal 2025. Thus, generic drug companies could see opportunities in the Japanese markets. With the higher expected demand for generics, big pharma companies in the country are coming together to form joint ventures to cater to this demand.

ABBREVIATED NEW DRUG APPLICATION APPROVAL IN JAPAN

The Office of Generic Drugs, 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.

At the time of generic drug application, documents regarding specifications, test methods, accelerated testing, and bioequivalence (BE) studies are required. In addition, the submission of long-term storage test data may be required if the drug stability cannot be assumed based on the original drug (e.g., polymorphic form differences, hydrate differences).

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. ^[11]

REVIEW TIMELINE FOR GENERIC DRUG APPROVAL IN JAPAN:-

FIRST ENQUIRY (5 MONTHS)	ANSWER PREPARING (1.5 MONTHS)	INQUIRY ANSWER (2.5 MONTHS)	GMP INSPECTION (3 MONTHS)
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APPROVAL JUDGEMENT PERIOD OF MHLW

12 MONTHS



COMPARISON OF ANDA APPROVAL PROCESS IN USA, EUROPE AND JAPAN

COMPARISON CATEGORY	UNITED STATES	EUROPE	JAPAN
AGENCY	United states Food and Drug Administration	European Medicines Agency	Pharmaceutical Medical Device Agency
AUTHORITIES INVOLVED IN REVIEW/GRANTING GENERIC DRUG APPROVAL	1. Centre for drug evaluation and research 2. Office of generic drugs.	1. European medical agency. 2. Committee for Human Medicinal Products 3. European union	1. Pharmaceutical Medical Device Agency 2. Office of generics 3. Ministry of Health Labour and Welfare
APPLICATION TYPE	Abbreviated new drug application.	Marketing authorisation Application.	New generic drug Application.
REGISTRATION PROCESS	One registration process	Multiple registration process 1. Centralised procedure 2. Decentralised procedure 3. Mutual recognition procedure 4. National procedure	One registration process
TIME FRAME	18 months	12 months	12 months
FEE STRUCTURE	\$70,480	£ 27,800	For every review meeting separate fees.
PRESENTATION FORMAT	Ectd	eCTD is mandatory for centralised procedure. For mutual recognition and DCP CTD and eCTD format are accepted.	Ectd

BIOEQUIVALENCE REQUIREMENTS IN US, EUROPE AND JAPAN FOR GENERIC DRUG APPROVAL

COMPARISON CATEGORY	UNITED STATES	EUROPE	JAPAN
SUBJECTS EMPLOYED IN BIOEQUIVALENCE STUDY	Healthy volunteers taken into account according to the age, sex, race. If the drug product is to be predominantly used in elders, then sponsor is recommended to include as many subjects as possible that are 60 years of age or older	Healthy volunteers not more than 12.	20 healthy volunteers.
BIOEQUIVALENCE AND BIOAVAILABILITY REQUIREMENTS PRESENTED IN LEGAL DOCUMENT	21 CFR PART 320	Directive 2001/83/EC, Article 10(1)	Guideline of bioequivalence testing for generic approval Framed by division of drugs (updated in 2012)
ACCEPTED BIOEQUIVALENCE LIMIT	80-125%	80-125%	80-125%
BIOEQUIVALENCE STUDY REQUIREMENTS	Fast /fed conditions against RLD/US innovator FDA approved center	Fast condition, against EU INNOVATOR (fed only if required)	Fasting/fed conditions, as recommended by PMDA/OGD
BIOEQUIVALENCE STUDY DESIGN	Two period, two sequence, two treatment, single dose cross over study	Randomised, two period, two sequence, single dose cross over design	Single-dose, cross over study

CONCLUSION

The generic market share is tremendously increasing in most of the countries; generic drugs are now becoming the strong competitors to the blockbuster drugs (or) branded drugs. The number of generic drug approval is steadily increasing year by year, due to their low cost and effective action equivalent to branded drugs.

From the above comparison, USA, EUROPE and JAPAN are following different approval procedures and each of them are unique in their own way. Europe has adopted 4 marketing authorisation procedures for the generic drug approval; the sponsor can apply for approval through any one procedure based on his drug. Europe safeguards the public health by assessing the medicines to their rigorous scientific standards. The USA follows stringent procedures to approve the generic drugs, it scrutinizes the generic drug application and the dossier submitted on support to application in a inflexible way so as to protect the public health and provide quality medicines. In Japan the generic drug approval process is taken care by ministry of labour health and welfare and office of generic drugs. The approval requirements are more or

less same in Japan as United States. The Japan differs from Europe and United States in their fee structure as it demands particular amount for every meetings carried on for the generic drug approval process.

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