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GENERIC DRUG APPROVAL PROCESS OF INDIA, JAPAN, USA

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ABSTRACT :

A regulatory process by which a person gets authority to launch a drug in the market, is known as drug approval process. ANDA is an application for a US generic drug approval for existing licensed medication or approval drug. Drug analyst in regulatory agencies around the world keep up the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of new drug product to serve the public health. Every country has it's own regulatory authority, which is responsible to implement the rules & regulations and issue the guidelines to regulate the marketing of the drug. This article focus on the drug approval process in different Countries like India, Japan and US -FDA.

Key words : US -FDA, India, Japan, ANDA, Regulatory approval processes

INTRODUCTION :

When patent exclusivity for drug names expires, an application for drug approvals can be submitted to US Food and Drug Administration (FDA). The FDA has published a list of drug names whose patent protection has expired in the "Drug Products Approved by Clinical Equivalence Assessment", commonly known as the Orange book. Defines FDA-approved drug products that are considered equivalent drugs in terms of safety and efficacy when administered to patients under the conditions listed on the label.[8]

a) Generic drug : According to the FDA, a generic drug is a product comparable to a precursor or standard drug product (usually a brand name drug) on the basis of dosage form, method of administration, potency, quality, understanding of safety, and good functioning. The generic drug must have the same intended use as the lead product on which it is based.

b) Bio-equivalence : Bio-equivalence drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet conspectus or other applicable standards (i.e., strength, quality, purity, and identity). Bio-equivalence (BE) is defined as the absence of a significant difference in the rate and extent in which an active ingredient or an active ingredient in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered in the same molar dose under similar conditions in an appropriately designed study.

c) Generics and Branded Drugs similarities & differences : FDA classifies generic drugs as therapeutically equivalent to standard drugs, and considered drug equivalents. Pharmaceutical ingredients, same dosage form, and method of administration confirm to guide standard and USP drug standards. Generic drugs must be bio-equivalent to brand drugs, have appropriate labels for correct use, and be manufactured in accordance with applicable Good Manufacturing Practices (GMP) regulations.The process of ANDA is the same as NDA, the only difference is that CDER and OGD (Office of Generic Medicines) review and review data for bio-equivalence studies, chemical or microbiological review, plant review and label review. If all parts determine that the generic meets all criteria under the guidelines, the generic drug will be approved for marketing.[16]

Table : 01 Comparison between NDA & ANDA requirements

NDA Requirement (Brand drug)	ANDA Requirement (Generic drug)
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. labeling	4. labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical studies	6. Bio-equivalence
8. Bio-availability	

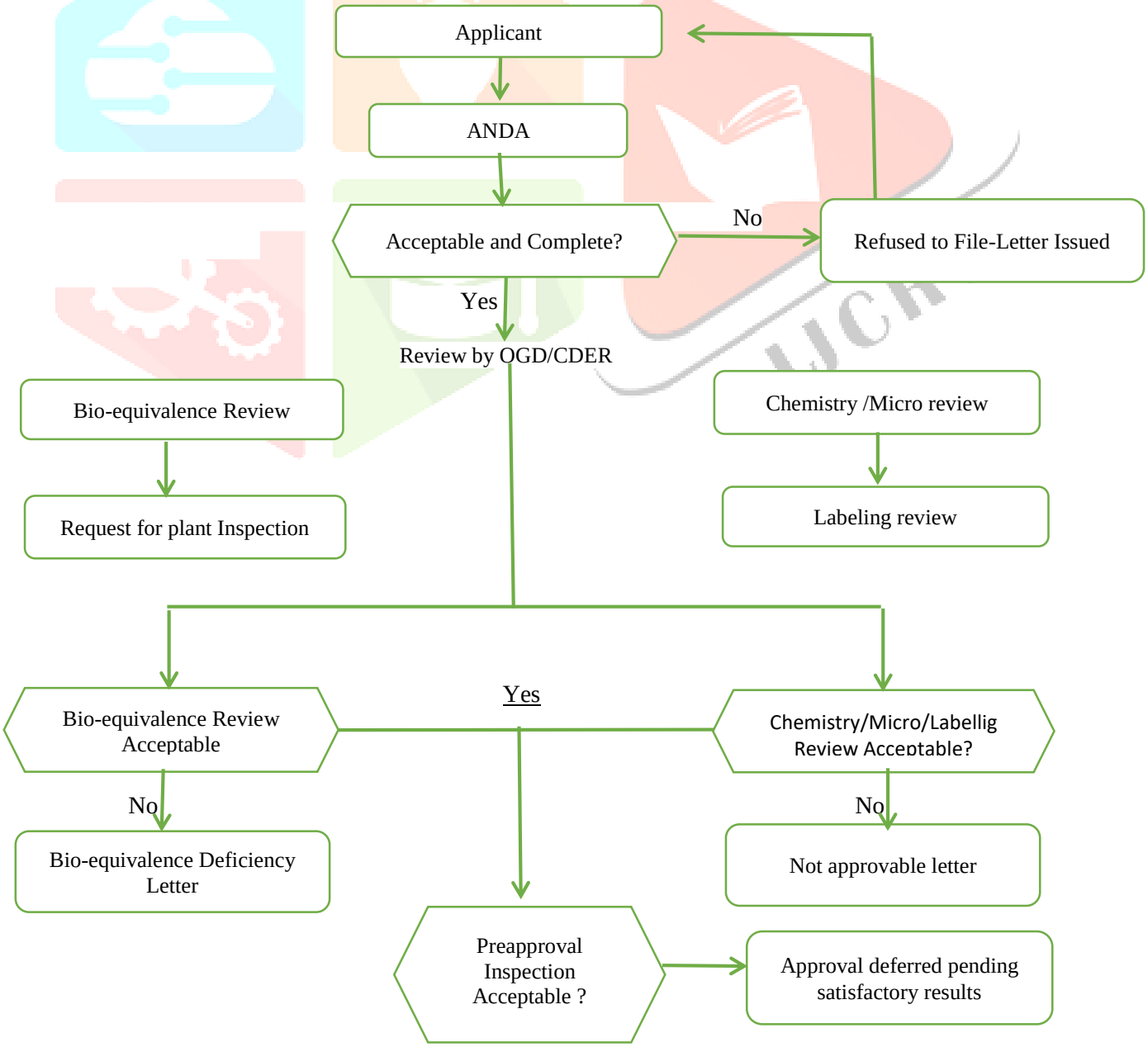

Fig. : 02 flow chart of ANDA approval process[4]

GENERIC DRUG APPROVAL PROCESS IN INDIA :

This application is completely different from the new drug application. In this application, CDSCO and DCGI may allow the applicant and regulatory authorities to rely on a portion of the safety and/or efficacy data for a previously approved drug. However, additional non-clinical and/or clinical data are required to substantiate new claims for an approved drug. Additional data needed to determine the safety and efficacy of the new generic drug are determined according to the new claim. If the drug is already approved by various agencies and is being marketed in major countries for the proposed new claim. If the generic drug proves its bio-equivalence and pharmaceutical equivalence with the approved drug and there is no change in metabolism due to ethnic difference. Animal toxicological and clinical data requirements may be reduced or relaxed if the proposed new claim concerns a serious life-threatening disease or a disease of special importance. CDSCO will review the reasonableness of such applications to grant approval for the manufacture/import of such new drugs. If necessary, the matter may also be examined after consultation with experts/committees of experts.[8]

❖ **Documents required for generic drug approval :**

Different types of documents are required to submit an abbreviated new drug application, which are listed below :

- Ingredients :
  - Bio-availability / Bio-equivalence
  - Name of examiner / center
  - Raw material source and stability
- Raw material :
  - Production method
  - QC parameters, specifications, stability
  - Toxicity to animals
- Fixed Dose Combination (FDC) Approval / Permit :
  - Justification
  - Pharmacokinetic /Pharmacodynamic data
  - Any other data
- Additional approval or approval of a new indication – new dosage forms :
  - Number and date of approval already granted
  - Justification
  - Safety, efficacy and quality data

GENERIC DRUG APPROVAL PROCESS IN USA :

Since the passage of the Hatch-Waxman Amendment in 1984, the FDA has approved more than 10,000 generic drugs. The shift from brand-name drugs to generics continues to increase every year. Currently, generic drugs account for about 65% of all prescriptions filled in the US. To market a prescription or over-the-counter generic drug, an Abbreviated New Drug Application (ANDA) must be submitted to the FDA Office of Generic Drugs (OGD). The OGD decides whether a certain generic product is therapeutically equivalent to its corresponding reference product (RLD). To be considered therapeutically equivalent to the

corresponding reference product, a generic product must provide evidence that it is pharmaceutically equivalent to the corresponding RLD, appropriately labeled, manufactured in accordance with current GMP regulations, and bio-equivalent to the RLD.

Reports that provide data from BE studies, which were conducted to compare the rate and extent of in vivo drug absorption of generic drugs and corresponding reference products, are a key component of ANDA submissions. Together with the determination of drug equivalence, the determination of BE enables regulatory conclusions about therapeutic equivalence. Equivalent generic products are therapeutically compatible with RLD. OGD Office of Bio-equivalence (DBE) reviews BE studies in applications received for new generic drugs.

a) ANDA Regulatory Review Process : The ANDA process begins when the applicant submits an ANDA to the OGD (Office of Generic Drugs) or CDER (Centre for Drug Evaluation and Research). Documentation staff files the ANDA and assigns the ANDA number and date of receipt to the ANDA cover letter. The ANDA is then sent to a consumer safety officer who reviews the preliminary ANDA verification form. Submitted ANDA will be reviewed considering chemical, pharmaceutical and microbiological and proprietary bio-equivalence. Complete a data review within the first 60 days of ANDA submission.[17]

b) Bio-equivalence Review Process : Two important features of generic drugs that are therapeutically equivalent to innovative drugs are drug equivalence and bio-equivalence. Both the innovative and generic drug must be pharmaceutically equivalent, that is, they must have the same strength, dosage form and method of administration. Products are said to be bio-equivalent if they have similar bio-availability when studied under the same conditions. Bio-equivalence is determined by evaluating the AUC and maximum concentration of the drug. A pharmaceutical product is considered bio-equivalent to the branded product if the mean AUC and 90% confidence interval (CI) for the relative mean C_{max} are 80% to 125%.[17]

c) Label Review Process : The Label Review Process is to ensure that brand-name drugs and drugs have the same labels. Applications will receive full approval or a letter of approval after the final stage of their review of the administration and individual disciplines for shortcomings. A completed approval letter outlines the approval conditions and authorizes the applicant to market the pharmaceutical product.An approved license is granted if the drug used (RLD) has a patent that has not expired or has been excluded.[17]

GENERIC DRUG APPROVAL PROCESS IN JAPAN :

Approval of generics in Japan is done by the Medicines Agency, which is affiliated with the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and is responsible for reviewing the approval of generics. The PMDA evaluates the equivalence of generic drugs and branded drugs for efficacy, efficacy and safety based on information submitted by drug applicants. There are two types of approval in Japan that is new generic drug and partial change approval. The new generic application is filed first and the partial change application is made only after certain changes have been approved. Suggested terms in Japan include instructions, functions, instructions, dosage, specifications, tests, storage methods, expiration dates, manufacture, ingredients or manufacturer, brand name, etc. Takes place.[6]

If the applicant's drug use name is changed after registration for content, in addition to minor changes, the PMDA must also review and approve certain changes.

Important information required for generic drug approval is given below :

- The manufacturing process, standards, and test methods used to evaluate specifications and test patterns (and some manufactures).
- Fixed data used for speed tests.
- Absorption, distribution, metabolism and excretion data for bio-equivalence assessment.

RESULT & DISCUSSION :

1) Administration :

Table : 02[6]

Sr No	REQUIRMENTS	USA	INDIA	JAPAN
1	Regulatory Authority	United Food And Drug Administration(US FDA)	Central Drug Standard & Control Organization (CDSCO)	Ministry of Health Labor and Welfare(MHLW)
2	Application	ANDA	MAA	NA
3	Debarment Certification	Required	NA	NA
4	No.of copies	3(archival, review, field)	1	Not specified
5	Clinical studies fees		50000 Rs.	654200 yen
6	Approval time line	18 months	12 months	12 months
7	Presentation	eCTD & paper	paper	eCTD

2) Manufacturing & Control :

Table : 03[6]

Sr. No	REQUIREMENTS	USA	INDIA	JAPAN
1	Batches	1	1	1
2	Packaging	A minimum of 100000 units	Not required	Not required
3	Process Validation	Not required at the time of submission	Required	Required

3) Finished Product Control :

Table : 04[6]

Sr. No	REQUIREMENTS	USA	INDIA	JAPAN
1	Assay	90-100 %	90-110%	90-111 %
2	Disintegration	Not required	Required	Required
3	Colour identification	Not required	Required	Required
4	Water content	Required	Required	Required

4) Stability :

Table : 05[6]

Sr. No	REQUIREMENTS	USA	INDIA	JAPAN
1	Date and time of the submission	3 months accelerated and 3 months long term	6 months accelerated and 3 months long term	6 months accelerated
2	Container orientation	Inverted upright	Do not address	Do not address
3	QP certification	Not required	Required	Required
4	Retention of sample	5 years from the date of filling the application	3 years from the date of filing the application	Not required

CONCLUSION :

Approval procedures in the United States, Japan, and India have similar goals and principles, but may have variations in their specific processes and requirements. Although the information does not specifically state that
procedures are "identical" or "same", meaning that both countries have strict standards and regulations drug approval with a focus on ensuring public health and safety. Each country has its own regulatory authorities
responsible for enforcing these standards and overseeing drug development, testing and manufacturing. in In summary, approval procedures in the United States, India, and Japan share common goals, but may have different approaches and criteria.

The United States has strict standards and procedures in place to ensure the safety and effectiveness of generic drugs. Regulatory bodies prioritize the public welfare and enforce guidelines for drug development, testing, clinical trials and manufacturing. The approval process includes a thorough review of generic applications and support documentation.

India is a major global manufacturer of generic drugs with a strong presence in the generic drug market. The country focuses on the production of generic drugs and plays a significant role in meeting the global demand for drugs.

In Japan, the Ministry of Health, Labor and Welfare, together with the Generic Medicines Agency, oversees the

generic drug approval process. While specific approval requirements are not listed, the Japanese government has set a target to achieve high utilization of generic drugs, which indicates a growing demand these drugs.

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