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REGULATORY REQUIREMENTS OF REGISTRATION OF GENERIC DRUGS IN USA

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Abstract:

A generic drug is more efficient, safe and low-cost alternative of the innovator or branded drug in the market. They are similar to the branded drugs in strength, quality, purity and their safety and efficacy have been proven since they have been in the market for a longer time. The availability of generic medicine should be made easier throughout the world. The US has one of the most demanding regulatory authorities and registration of drug products will be a long process if not complied with the US Food and Drug Administration (USFDA) guidelines. Abbreviated New Drug Application is the application to be filed for registering generic drug. One of the main tasks of the regulatory authorities is to ensure that the drug development, manufacture and testing has been carried out according to the regulations and guidelines and that everything is documented accordingly. International Conference on Harmonization (ICH) established a harmonized format for submission of application on registering drug products.

Keywords: *Generic Drug, Abbreviated New Drug Application (ANDA), US Food and Drug Administration (USFDA) guidelines.*

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INTRODUCTION: [1-4]

A generic drug is a drug defined as "a drug product that is comparable to a brand/ reference listed drug product in dosage form, strength, quality and performance characteristics and intended use". Any drug that is marketed by its chemical name rather than advertising its brand name or chemical make-up is referred to as a generic drug. Even though they are not under any particular company they are subjected to regulation by the authorities of the government of that country. The US Food and Drug Administration (FDA) considers a generic drug to be "identical, or bioequivalent, to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use".

The safety and efficacy of the original active ingredient was already proven, the bio equivalence of the equivalent generic drug should be checked by the manufacturer.

US FOOD AND DRUG ADMINISTRATION (USFDA):

The USFDA is a scientific, regulatory and public health agency that jurisdiction encompasses on most food products (other than meat and poultry), human and animal drugs, therapeutic agents of biological origin, medicinal devices, radiation-emitting products for consumer, medical occupational use, cosmetics and animal feed. The Office of the Commissioner heads the organization under which there are four departments overlooking management, health, and science, international activities and regulatory affairs. They have various centers for regulation of medicinal products, medical devices, food, veterinary products and also toxicological research. The FDA is also responsible for advancing the public health by helping to spend innovations that make medicines and food more effective, safer, more affordable and helping the public to get proper, scientific information about the food and medicines to improve their health.

ABBREVIATED NEW DRUG APPLICATION (ANDA) [5-8]:

The Documents or the application submitted to the FDA for the approval of a generic drug product is known as an Abbreviated New Drug Application or ANDA. It contains all the data for FDA review and approval. Once the ANDA is approved the manufacturer can market the safe, effective and less expensive generic version. To be approved by FDA, the amount of active ingredients in the circulatory system of the patient should be same for both the generic and the innovator drug. Enactment of the Drug Price Competition and Patent Restoration Act of 1984, better known as "The Hatch- Waxman Act" is the major force for generic market development in the US. It has created opportunities for developing and marketing generics or better called anabbreviated new drug application for 180 days. Final approval of ANDA by the FDA takes minimum18 months.

Common Technical Document (CTD):

CTD is a common technical document, it is a harmonized document introduced by the ICH in order to avoid any duplication and easier translation into regional languages in a single application. CTD makes it easier to submit one single application to more than one country at the same time for registration of the drug product. According to ICH, all the technical requirements for the application of drug approval were harmonized in CTD.

The main Areas of Harmonization for CTD are:

- Safety pharmacology
- Clinical pathology
- Immunotoxicology
- Juvenile toxicology studies
- Statistical methods in certain studies like mutagenicity, carcinogenicity and toxicokinetic studies.

The different modules are as follows:

Module 1: This module is specific to each region and is usually not part of the CTD. It contains all the administrative information and prescribing information (package inserts and labeling) with respect to the regulatory agency of that particular country.

Module 2: It consists of the overviews and overall summaries of the CTD. Quality overall summaries, clinical and non-clinical overview and summaries are included in this module.Pharmacology, pharmacokinetics, toxicology studies which are important to prove the safety and efficacy of the drug.

Module 3: Quality – It covers the complete pharmaceutical and technical aspects which can affect the quality of the drug product. From the formulation and development department (pharmaceutical development report) to the manufacturing (GMP), analysis and testing (GLP), packing, storage conditions, stability studies of the product.

Module 4: Non-clinical study reports – It covers the complete pharmacological, toxicological study reports and information equivalent to the quality of the drug to provide the evidence of the safety of the drug product.

Module 5: Clinical study Reports – The results of various clinical trials on human beings and the reports listing the desired effect of the drug product are mentioned in this part. This part proves the efficacy of the drug to the regulatory authorities.

Bioequivalence studies are conducted on healthy volunteers to prove CTD triangle. the bioavailability similarity between the both generic and innovator drugs. Before CTD/eCTD application for the submission of a drug application, the procedure was different.

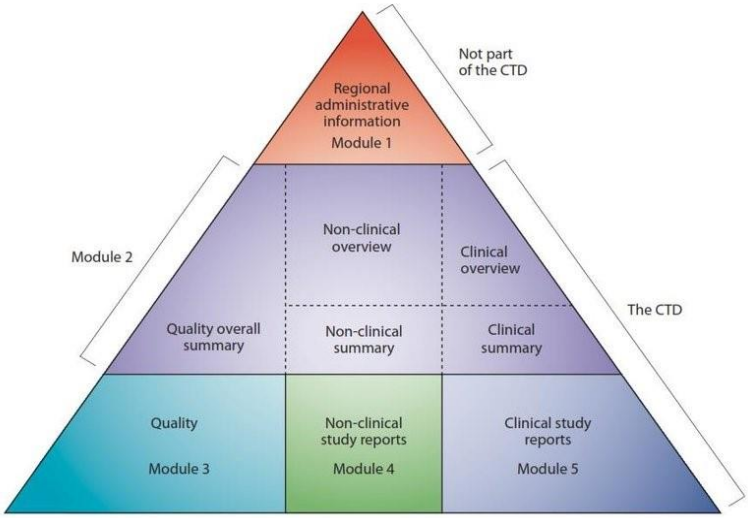

Fig-1- Common Technical Document (CTD)

Generic Drug Product Registration Requirements in the US [9-12]

1. The eCTD is mandatory for the submission of the drug applications (NDA/ANDA).

2. US FDA guidance (CFR) documents and FDA sections (e.g. 505 (b) for NDA and 505(j) for ANDA) are followed for the preparation of the dossier for the drug approval applications.

3.The applications are different as follows:

- For new drug- NDA
- For generic drug – ANDA
- For biological application – BLA

4. The applicant himself or a GDEA (Generic Drug Enforcement Act) certified and approved agent may directly submit the application to the FDA.

5. Administrative information is different from a cover letter, forms (356h), application information, field copy certification, debarment certification, financial certification, Patent information, and exclusivity.

6. The paper size for the submission is Letter size (8.5x11 inches) with font size 12 in times new roman format. The tables and figures have small font size i.e. 8 to 10.

7. Package inserts are provided for drug product in labeling.

8. Proposed Labels and cartons with proper dimensions similar to that of the RLD (Reference Listed Drugs) labels are provided.

9. The information about the clinical investigators is provided in Module 5 and in financial disclosure Statement section of this module.

10. Request for waiver of in-vivo BE studies is provided in module 1.

11. Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided.

12. The EAS (Environment Assessment Statement) for categorical exclusion certification in compliance with the law of EPA (Environment Protection Act) of US is provided.

13. Risk management Plans section is for the post marketing surveillance and controlling the adverse effects of the drugs by proper management. This is the part of Clinical Trial Phase IV.

14. The declaration is given for the residual solvents limits used or present in the drug substance and excipients according to the USP.

15. Information on components including the name and address of the supplier or manufacturer of the raw material, package material etc.

16. Certificate of suitability (CEP certificate) is not applicable.

17. Comparability protocols are not attached to both the drug substance and drug products.

ANDA Regulatory Review Process [12-14]:
The ANDA process begins when an applicant submits an ANDA to the OGD (Office Generic Drugs) or CDER (Centre for Drug Evaluation and Research). The document room staff process the ANDA assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA checklist. The submitted ANDA is reviewed taking into consideration bioequivalence of the drug, chemistry

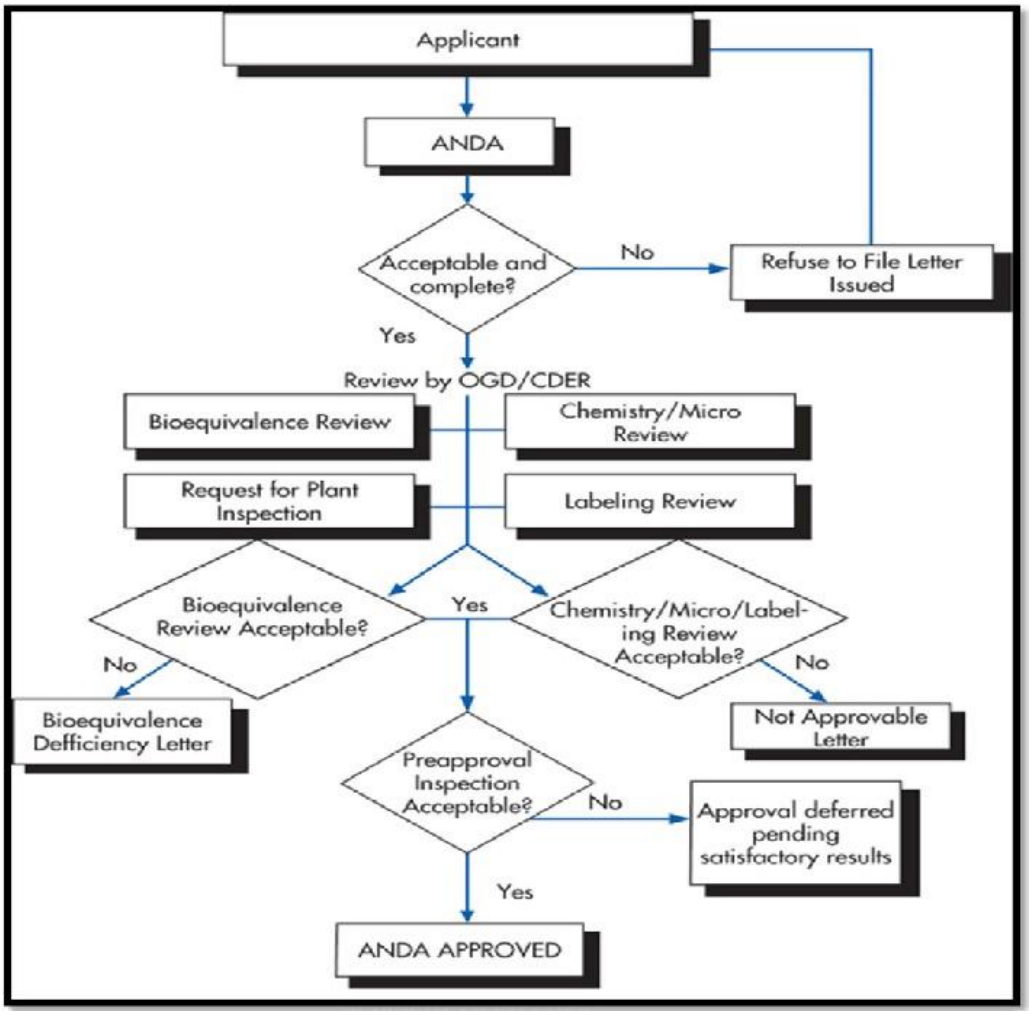

Fig-2- ANDA Review Process

Bio Equivalence Review Process:
The two main characteristics of a generic drug to be therapeutically equivalent to the innovator drug are to be pharmaceutically equivalent and also bioequivalent. Both the innovator and generic drug should be pharmaceutically equivalent i.e. they should have the same strength, dosage form and same route of administration. The products are said to be bioequivalent when they have similar bioavailability when they are studied under same condition. Bioequivalence is determined by evaluation of the AUC and the maximum concentration of drug (Cmax). A generic product is considered to be bioequivalent to the branded product if the 90% confidence interval (CI) of the mean AUC and the relative mean Cmax is 80% to 125%.

Labeling Review Process:
The labeling review process is to ensure that both the innovator and the generic drug have the same labeling. After the final level administrative review and individual disciplines have resolved their

deficiencies, the application will either receive a full approval or a tentative approval letter. A full approval letter details the conditions of approval and allows the applicant to market the generic drug product. A tentative approval letter is issued if there are unexpired patents or exclusivities accorded to the Reference Listed Drug (RLD).

CONCLUSION:

The United States has the most stringent regulation for generic drug filing in the world. The regulatory authorities should ensure that the pharmaceutical companies comply with the FDA regulations and guidelines. There are regulations and guidelines that help in drug development, manufacture, and safety testing so that they are safe and efficient and do not harm the patient's well-being. CTD provides a globally harmonized format that is accepted in many regions, avoiding the need to compile different registration dossiers for different regulatory authorities. Countries have different standards; there are high registration costs and long timelines for registration of generic drugs. This may account for the good market share of generics in the USA.

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