Regulations on API, novel drugs and Biologics

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INTRODUCTION

- Active pharmaceutical ingredients (API) are the constituents which gives medical products are their pharmacological activity. For this reason the quality and the stability of APIs are crucial factors in the overall quality, safety and efficacy of medicinal products.
- Regulatory guidelines is an organization`s adherence to law`s, regulations guidelines and specifications relevant to its business.

- Since APIs are the compounds that actually provide the activity and effectiveness of all drugs, they are subject to a significant amount of review during the filing and approval processes.
- In order to obtain a marketing authorisation for a drug product the applicant has to show evidence of efficacy, safety and quality of the drug product.
- To assure this, appropriate documentation on the active substance including the manufacturing of the active substance has to be submitted to the competent authority.
- Different regions have adopted different procedure for regulatory filing for API, in U.S it as done as per DMF procedure of FDA while in Europe it is done by ASMF procedure.

Drug Master File or DMF

- A drug master file is a confidential, detailed document submitted by Active Pharmaceutical Ingredient (API) manufactures to the U.S Food and Drug Administration (FDA).
- It is also called as Active Substance Master File.
- There is no regulatory requirement to file a DMF. However, the document provides the regulatory authority with confidential, detailed information about **facilities, processes, or articles used in the manufacturing, processing, packaging, and storing** of one or more human drugs.

Types of DMFs

- Type I :Manufacturing site facilities, operating procedures, and personnel.
- Type II : Drug substance, drug substance intermediate, and uses in their preparation or drug product.
- Type III : Packaging Material.
- Type IV : Excipient, colorant , flavor, material used in their preparation.
- Type V : FDA accepted reference information.

Registration procedure for API in U.S.

- DMFs have no legal or regulatory basis in the United States; however, they do provide companies a relatively easy and confidential way to provide confidential information about a process without making it available to other commercial companies.
- The DMF should contain all of the detailed information expected by the regulatory authorities so that a DMF reference in an NDA or ANDA can be used to complete an agency review process. In the United States there is no approval process for a DMF.
- In fact, DMFs are only examined when referenced in other regulatory filings, such as an NDA or ANDA; only then is the content of a DMF reviewed. If requested by FDA headquarters, an FDA inspection may take place at an API manufacturing site after a review of the DMF.

Registration requirements of DMF

- Each DMF submission should contain

A. Transmittal letter

B. Administrative information about the submission

A. Transmittal Letters- The following should be included:

1.Original Submissions

2.Amendments

1. Original submissions

i. Identification of submission.

ii. Identification of the applications, if known, that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document numbers

iii. Signature of the holder or the authorized representative.

iv. Typewritten name and title of the signer.

2. Amendments

a. Identification of submission: Amendment, the DMF number, type of DMF, and the subject of the amendment.

b. A description of the purpose of submission, e.g. updates, revised formula, or revised process.

c. Signature of the holder or the authorized representative.

d. Typewritten name and title of the signer.

B. Administrative Information

- Administrative information should include the following:

1.Original Submissions

2.Amendments

Original Submissions:-

1. **Names and addresses of the following:**

i. DMF holder.

ii. Corporate headquarters.

iii. Manufacturing/processing facility.

iv. Contact for FDA correspondence

2. Amendments

a) Name of DMF holder.

b) DMF number.

c) Name and address for correspondence.

d) Affected section or page numbers of the DMF.

Rules for approval of a novel drug

- FDA approval of a drug means that data on the drug's effects have been reviewed by CDER, and the drug is determined to provide benefits and potential risks for the intended population.

Biologics / Biological product

DEFINITION:

Biological product is a virus, therapeutic serum, toxin, antitoxin, vaccine, blood component or derivatives, allergenic product or analogous product , applicable to the prevention ,treatment or cure of a disease or condition of human beings.

Rules for biological product approval

- As per FDA, the **Blood Establishments registration** should follow:-
- All owners or operators of establishments that manufacture blood products are required to register with the FDA.
- A list of every blood product manufactured, prepared, or processed for commercial distribution must also be submitted.
- Products must be registered and listed within 5 days of beginning operation, and annually between November 15 and December 31. Blood product listings must be updated every June and December.

LAW or ACT

- Drug product fall under the Food, Drug and Cosmetic Act.
- Biological products fall under the Food Drug and Cosmetic Act & Public Health Services Act.

Novel Drugs With Its Regulatory Requirements

- Novel drugs are often innovative products that serve previously unmate medical needs and significantly help to advance patient treatments.
- Noval drugs can represent important new therapies for advancing patient care.
- In 2017 CDER gave approval to many noval drugs includes as ;

  - **Dupixent :** to treat adult with moderate-to severe eczema (atopic dermatitis).

Rules for approval of a novel drug:

- FDA approval of a drug means that data on the drug's effects have been reviewed by CDER.
- The drug is determined to provide benefits that outweigh its known and potential risks for the intended population.
- These approaches can includes more interaction between CDER staff and drug developers, and shortened timelines for review of application.
- The drug approval process takes place within a structured framework that includes:

Analysis of the target condition and available treatments-

- FDA reviewers analyse the condition or illness for which the drug is intended and evaluate the current treatment landscape, which provide the context for weighing the drug's risks and benefits.

Assessment of benefits and risks from clinical data—

- FDA reviewers evaluate clinical benefit and risk information submitted by the drug maker,

Strategies for managing risks—

- All drugs have risks. Risk management strategies include on FDA-approved drug label, which clearly describes the drug's benefits and risks, and how the risks can be detected and managed.

Newer Approach- Faster Testing & Approval

- The mechanisms speed up the approval process, and apply a degree of flexibility with respect to the evidence requirements for the approval of certain medicines.

- In the U.S., accelerated pathways (APs) include **Fast Track (FT), Breakthrough Therapy Designation (BTD), Accelerated Approval (AA), and Priority Review (PR).**

Fast Track (FT):

- Fast track is a process designed to facilitate the development of drugs to treat serious or prevent a condition.
- If there are available therapies, a fast track drug must show some advantage over available therapy.
- Avoiding serious side effects of an available therapy
- Improving the diagnosis of a serious condition.

Breakthrough Therapy (BT):

- Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease.
- A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms.
- An effect on an established surrogate endpoint.
- A significantly improved safety profile compared to available therapy (eg :- less dose-limiting toxicity for an oncology agent)

Priority Review (PR):

- Prior to approval, each drug marketed in the United States must go through a detailed FDA review process.
- Under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – Standard Review and Priority Review.
- A Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

NEW DRUG APPROVALS

DEFINITION :-

- It is a regulatory mechanism that is designed to give Food and Drug Administration (FDA)sufficient information to make a meaningful evaluation of a New Drug.
- New Drug Application is the vehicle in the United States through which the drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing.

OBJECTIVES

Upon the completion of this presentation student gets to learn

- To know the approval process of NDA
- Drug development process
- concepts of innovator and generic drugs

CLINICAL TRIALS :-

- ✓ 10-15 years from lab to US patients.
- ✓ Only 1 in 5000 compounds make it to the human testing.
- ✓ Only 1 in 5 tested in humans is approved.
- ✓ Testing phases in Humans
    a) Discovery
    b) Development
    c) Clinical Studies
    d) Medicine approved

HISTORY

- ✓ When the federal food, drug and cosmetic act 1938 was passed, a new era of drug product development began.
- ✓ The act required the assurance of safety and stated minimum requirements for manufacturing and quality control.
- ✓ It provided only 60 days for review by FDA before the distribution of any new drug product.

GOAL :-

- ✓ Safety and effectiveness of a drug in its proposed use.
- ✓ Whether the drug proposed labelling (package insert) is appropriate.
- ✓ Methods used in manufacturing the drug and the controls used to maintain the drugs quality are adequate to preserve the drugs identity, strength , quality and purity.
- ✓ The benefits of the drug outweigh the risks.

REFERENCE

- http://www.slideshare.net/sidduKMI/regulatory-requirement-for-api-registration?from_m_app=android
- http://www.slideshare.net/RajeshKMI/regulatory-requirement-for-api-registration?from_m_app=android
- http://www.slideshare.net/abhinav/regulatory-requirement-for-api-registration?from_m_app=android
- http://youtu.be/yyGZcxWDK9Y