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First Test Examination – October - 2017

Branch: M.Pharm (Pharmaceutics) Sem.:- I
Subject with Subject Code: - Pharmaceutical Regulatory Affair (MPH103T) Marks: 20
Date: - Time:- 1.30 Hr.

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Instructions:-

(Marks)

Q.No.1 ***Attempt any five of the following (5 X 2)*** ***(10)***

(Objective type questions)

a) Define CFR.

The ***Code of Federal Regulations*** (***CFR***) is the codification of the general and permanent rules and regulations published in the *Federal Register* by the executive departments and agencies of the federal government. The CFR is divided into 50 titles that represent broad areas subject to federal regulation.

b) What is IND?

The United States Food and Drug Administration's Investigational New Drug(IND) program is the means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk. If the application is cleared, the candidate drug usually enters a Phase 1 clinical trial. Regulations are primarily at 21 C.F.R. 312.

c) What is 180 days exclusivity?

This guidance is intended to provide information on how the Food and Drug Administration (FDA) intends to determine eligibility for 180-day generic drug exclusivity when, on the same day, more than one applicant submits an abbreviated new drug application (ANDA) for the same drug under section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act) containing a paragraph IV certification to a listed patent, and no paragraph IV certification to the patent was submitted on any previous day. To date, FDA's exclusivity decisions have involved applications or amendments submitted on different days. This guidance explains why and how the Agency intends to apply a multiple first applicant approach.

d) What is Para IV Certification?

An ANDA applicant must include in its ANDA a patent certification as described in section 505(j)(2)(A)(vii) of the Act. The certification must make one of the following statements: (1) such patent information has not been filed; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be

infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted.
The fourth certification is known as a paragraph IV certification.
The ANDA applicant must provide appropriate notice of a paragraph IV certification to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA refers.

e) Define batch.

"Batch (or lot)
A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval".

f) Define SOP.

"A Standard Operating Procedure is a document which describes the regularly recurring operations relevant to the quality of the investigation. The purpose of a SOP is to carry out the operations correctly and always in the same manner. A SOP should be available at the place where the work is done".
Or
A standard operating procedure, or SOP, is a set of step-by-step instructions compiled by an organization to help workers carry out complex routine operations. SOPs aim to achieve efficiency, quality output and uniformity of performance, while reducing miscommunication and failure to comply with industry regulations.

g) Define Master Formula.

An approved master document, that describes the full process of manufacturing for the batch of product with at least cross-reference to the support operations for a batch of a specific product. Individual companies may give internal names to these documents (manufacturing instructions, monographs, etc).

Q.No. 2 Attempt any two of the following: (2 X 5) (10)

(Short answer questions 5 marks each)

a) Explain *eCTD* modules

The electronic common technical document (eCTD) is an interface and international specification for thepharmaceutical industry to agency transfer of regulatory information. The specification is based on the Common Technical Document (CTD) format and was developed by the International Conference on Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). ----- *(1 Mark)*

History:

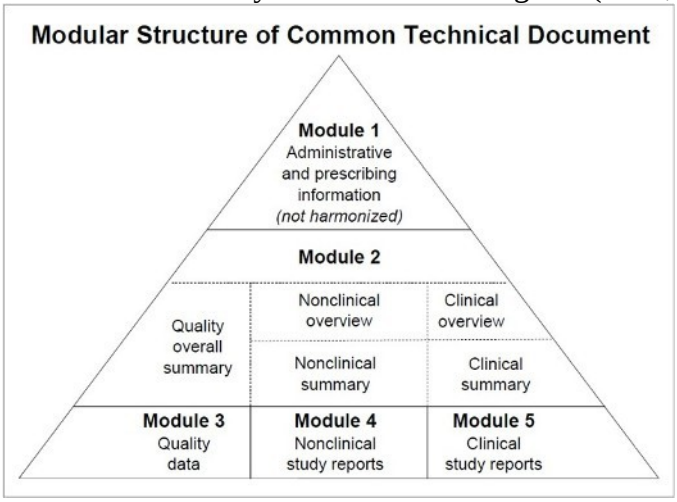
Version 2.0 of eCTD – an upgrade over the original CTD – was finalized on February 12, 2002,and version 3.0 was finalized on October 8 of the same year. As of August 2016, the most current version is 3.2.2, released on July 16, 2008.

A Draft Implementation Guide for version 4.0 of eCTD was released in August 2012. However, work stalled on the project. An additional Draft Implementation Guide was released in February 2015. Draft specifications and guides were issued in April 2016 by the ICH and the FDA, followed by a May 13 ICH "teleconference to discuss the guidance and any questions and clarifications needed.---------- *(1 Mark)*

Governing Specifications:
An eCTD submission's structure is largely defined by the primary standard created by the ICH, the Electronic Common Technical Document Specification. However, additional specifications may be applied in national and continental contexts. In the United States, the Food and Drug Administration (FDA) layers additional specifications onto its requirements for eCTD submissions, including PDF, transmission, file format, and supportive file specifications. In the European Union, the European Medicines Agency's EU Module 1 specification as well as other QA documents lay out additional requirements for eCTD submissions. ---------- *(1 Mark)*

The eCTD has five modules: ---------- *(02 Marks)*
Administrative information and prescribing information
Common technical document summaries
Quality
Nonclinical study reports
Clinical study reports

There are two categories of modules:
Regional module: 1 (different for each region; i.e., country)
Common modules: 2–5 (common to all the regions)
The CTD defines the content only of the common modules. The contents of the Regional Module 1 are defined by each of the ICH regions (USA, Europe and Japan).



b) Discuss Hatch Waxman Act.

Formally known as the Drug Price Competition and Patent Term Restoration Act of 1984, P.L. 98-417, to expedite and streamline both generic drug approvals and patent litigation involving generic drugs. ---------- *(1 Mark)*
Enacted in 1984
Amended the Patent laws
Amended the Federal Food, Drug, and Cosmetic Act
Before 1962- new drug approved based on safety alone

1962- Proof of efficacy made compulsory for marketing approval of a new drug (Kefauver-Harris Amendments)

There was no provision for patent term extension prior to enactment of the Hatch Waxman Act, to make up for the time lost out of the total patent term during the marketing approval process

Generic companies required to submit their own comprehensive NDA

Costly

Time consuming

If drug was covered by patent

Testing could not begin until patent expired

To overcome the above problems an act was needed to promote generic companies

Objectives of The Act ---------- *(2 Marks)*

Reducing the cost associated with the approval of a generic drug

Allowing Early-Experimental-Use

Compensating the branded drugs manufacturers for the time lost from the patent term because of the regulatory approval formality

Motivating the generic drug manufacturers

Provisions of The Act ---------- *(2 Marks)*

Creation of section 505(j)

Section 505(j) established the ANDA approval process

The timing of an ANDA approval depends in part on patent protections for the innovator drug

NDA must include any patent that claims the "drug" or a "method of using [the] drug" for which a claim of patent infringement could reasonably be asserted

On approval of NDA, FDA publishes patent information for drug in Orange Book ("Approved Drug Products with Therapeutic Equivalence Evaluations")

c) How post marketing surveillance is carried out?

Postmarketing surveillance (PMS) (also post market surveillance) is the practice of monitoring the safety of apharmaceutical drug or medical device after it has been released on the market and is an important part of the science of pharmacovigilance. Since drugs and medical devices are approved on the basis of clinical trials, which involve relatively small numbers of people who have been selected for this purpose – meaning that they normally do not have other medical conditions which may exist in the general population – postmarketing surveillance can further refine, or confirm or deny, the safety of a drug or device after it is used in the general population by large numbers of people who have a wide variety of medical conditions.

Postmarketing surveillance uses a number of approaches to monitor drug and device safety, including spontaneous reporting databases, prescription event monitoring, electronic health records, patient registries, and record linkage between health databases. These data are reviewed to highlight potential safety concerns in a process known as data mining. ---------- *(1 Mark)*

Thus, four types of studies are generally used to identify drugs effects: 1. Controlled clinical trials, 2. Spontaneous or voluntary recording 3. Cohort studies and 4. Case control studies ---------- *(4 Marks)*

1. **Controlled clinical trials:** To minimize bias through such method as randomization and “double-blinding‟”. Directly monitor patients for the duration of studies. For evaluating a drug‟s efficacy and safety. They are often costly
2. **Spontaneous or voluntary reporting** By physician and other health providerϖ & hospital may to alert FDA and pharmaceutical firms to possible adverse effects of drugs.
3. **Cohort studies**: Studies follow a defined group of patient for a period of time. Patients are not randomly assigned & there is no blinding. If adverse reaction occur. A second group of patient with the same medical condition, who are not taking the drug and who may be receiving alternative treatment.
4. **Case-control studies**: Case control studies identify patient with the adverse effects to be studied, and compare them with the sample drawn from the same cohort that gave rise to cases.

Q.No. 3 Attempt any one of the following. (1 X 10) (10)

(Long answer questions 10 marks)

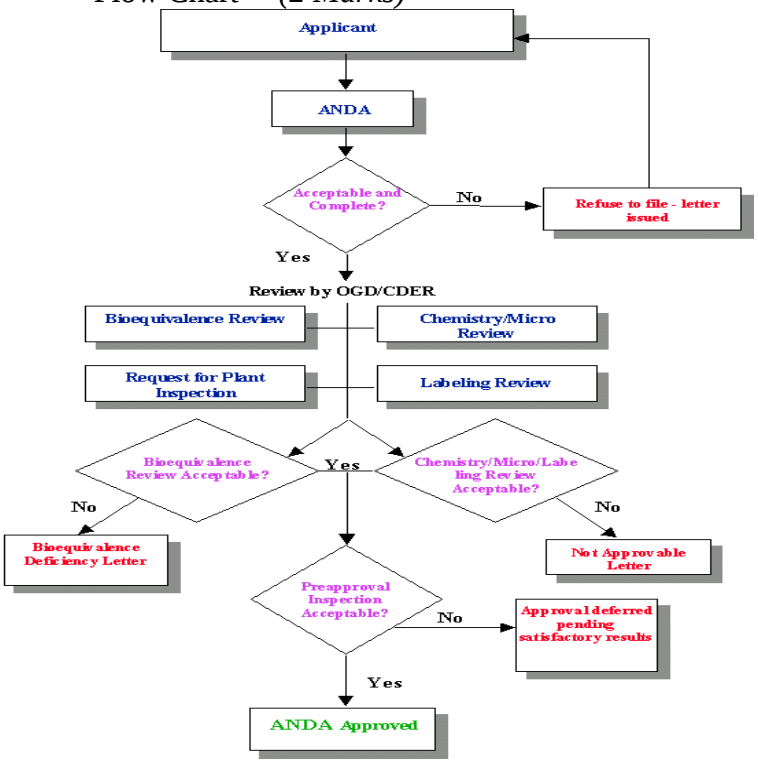
a) Discuss regulatory approval process for ANDA.

Introduction & overview: ---*(2 Marks)*

Steps: *(1 Mark each step)*

1. Filling review
2. Coordination of generic drug review process.
3. Bioequivalence review process.
4. Chemistry review process.
5. Labeling review process.
6. Putting it all together.

Flow Chart ---*(2 Marks)*



b) Discuss regulatory requirement biological approval

The Definition of “Biological Product” and Its Significance ---*(1 Mark)*

Nonclinical Studies for Biologics ---*(3 Marks)*

- Relevant Species
- Immunogenicity
- Typical Preclinical Testing

Clinical Studies for Biologics ---*(3 Marks)*

- The Investigational New Drug Application
- Good Clinical Practices
- Study Design Considerations
- Manufacturing Process Changes during Development
- Meetings with the Food and Drug Administration Before and During the Clinical Trial Period S

The Biologics License Application ---*(3 Marks)*

- Contents of the Biologics License Application
- Food and Drug Administration Review
- Approval Standard