UNIT-V

Regulatory Concepts

Points to be covered in this topic

- ❑ Basic terminology
- ❑ Guidance, Guidelines & Regulations
- ❑ Laws and Acts
- ❑ Orange book
- ❑ Federal Register
- ❑ Code of Federal Regulations
- ❑ Purple Book

Basic terminology

❑ Regulatory Affairs :

- "Regulatory Affairs" in a pharmaceutical industry, is a profession which acts as the interface between the pharmaceutical Industry and Drug Regulatory Authorities across the world. It is mainly involved in the registration of the drug products in respective countries prior to their marketing.

❑ Investigational New Drug (IND) Application :

It is an application which is filled with FDA to get approval for legally testing an experimental drug on human subjects in the USA.

❑ New Drug Application (NDA) :

The NDA is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational new drug become part of the NDA.

❑ Abbreviated New Drug Application (ANDA) :

It is an application filed with FDA, for a U.S. generic drug approval for an existing licensed medication or approved drug.

❑ Generic Drug Product :

A generic drug product is the one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use.

❑ Drug Master File (DMF) :

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes or articles used in the manufacturing, processing, packaging and storing of one or more human drugs.

❑ Marketing Authorization Application (MAA) :

It is an application filed with the relevant authority in the Europe to market a drug or medicine.

❑ Active Substance Master File (ASMF) :

Active substance master file is a submission which is made to EMA, MHRA or any other Drug Regulatory Authority in Europe to provide confidential intellectual property or 'know-how' of the manufacturer of the active substance.

❑ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) :

It is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

❑ Common Technical Document (CTD) :

It is a set of specification for application dossier, for the registration of Medicines and designated to be used across Europe, Japan and the United States. Quality, safety and Efficacy information is assembled in a common format through CTD. The CTD is maintained by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

❑ Orange Book :

It is the commonly used name for the book "Approved Drug Products with Therapeutic Equivalence Evaluation" which is published by USFDA.

It contains the list of drug products, approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug and Cosmetic Act.

❑ Hatch-Waxman 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 amendment of the federal food, drug and cosmetics act established the process by which, would be marketers of generic drugs can file Abbreviated New Drug Application (ANDA) to seek FDA approved of generic drugs.

❑ Patent Certification under Hatch-Waxman Act :

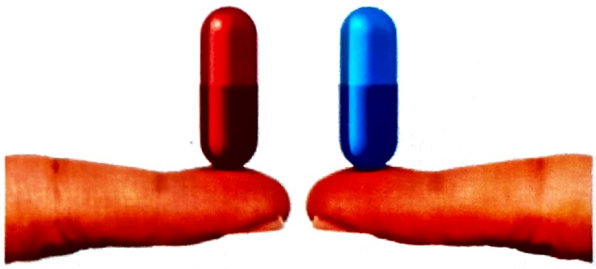
As per the Hatch-Waxman Act, generic drug and 505 (b) (2) applicants should include certifications in their applications for each patent listed in the "Orange Book" for the innovator drug. This certification must state one of the following :

(i) That the required patent information relating to such patent has not been filed (Para I certification).

(ii) That such patent has expired (Para II certification).

(iii) That such patent will expire on a particular date (Para III certification).

(iv) That such patent is invalid or will not be infringed by the drug, for which approval is being sought (Para IV certification).



❑ 180-days exclusivity :

The Hatch-Waxman Amendments provide an incentive of 180 days of market exclusivity to the "first" generic applicant who challenges a listed patent by filling a paragraph IV certification and thereby runs the risk of having a defend patent infringement suit.

❑ Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) :

It is the certificate which is issued by Certification of substances Division of European Directorate for the Quality of Medicines (EDQM), when the manufacturer of a substance provides proof that the quality of the substance is suitably controlled by the relevant monographs of the European pharmacopoeia.

❑ Current Good Manufacturing Practice (cGMP) :

It is a practice and the systems required to be adapted in pharmaceutical manufacturing, quality control, quality system covering the manufacture and testing of pharmaceuticals or drug including; active pharmaceutical ingredients, diagnostics, food, pharmaceutical products and medical devices.

❑ Good Clinical Practice (GCP) :

It is the international quality standard that is provided by International Council for Harmonisation (ICH) that defines standards, which governments can transpose into regulations for clinical trials involving human subjects.

Guidance, Guidelines & Regulations

Indian Regulations & Guidelines

CDSCO	Central Drugs Standard Control Organization (CDSCO), Ministry of Health & Family Welfare, Government of India provides general information about drug regulatory requirements in India.
NPPA	Drugs (Price Control) Order 1995 and other orders enforced by National Pharmaceutical Pricing Authority (NPPA), Government of India.
D & C Act, 1940	The Drugs & Cosmetics Act, 1940 regulates the import, manufacture, distribution and sale of drugs in India.
Schedule M	Schedule M of the D&C Act specifies the general and specific requirements for factory premises and materials, plant and equipment and minimum recommended areas for basic installation for certain categories of drugs.
Schedule T	Schedule T of the D&C Act prescribes GMP specifications for manufacture of Ayurvedic, Siddha and Unani medicines.
Schedule Y	The clinical trials legislative requirements are guided by specifications of Schedule Y of the D&C Act.
GCP guidelines	The Ministry of Health, along with Drugs Controller General of India (DCGI) and Indian Council for Medical Research (ICMR)has come out with draft guidelines for research in human subjects.
The Pharmacy Act, 1948	The Pharmacy Act, 1948 is meant to regulate the profession of Pharmacy in India.
The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954	The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954 provides to control the advertisements regarding drugs; it prohibits the advertising of remedies alleged to possess magic qualities.
The Narcotic Drugs and Psychotropic Substances Act, 1985	The Narcotic Drugs and Psychotropic Substances Act, 1985 is an act concerned with control and regulation of operations relating to Narcotic Drugs and Psychotropic Substances.

Laws and Acts

Various laws and ethics govern pharmacy operations. While the laws are the legal framework within which a pharmacy and its personnel can operate, ethics are professional regulations, which govern a pharmacist in operating a pharmacy Laws related to Community Pharmacy

1. The Drugs and Cosmetics Act, 1940 and Rules, 1945
2. The Narcotic Drugs and Psychotropic Substances Act and Rules, 1985.
3. Drugs Price Control Order, 1995
4. Consumer Protection Act, 1986
5. Infant Milk Substitutes, Feeding Bottles and Infant Foods Act, 1992
6. Drugs and Magic Remedies Act and Rules, 1954.
7. Prevention of Food and Adulteration Act, 1954.

Orange Book

It is the publication of "Approved Drug Products with Therapeutic Equivalence Evaluations" by the Food and Drug Administration. It is prepared by The Orange Book Staff, Center for Drug Evaluation and Research. It identified drug products on the basis of safety and effectiveness by the Food and Drug Administration under the Federal Food, Drug, and Cosmetics Act.

The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. The FDA does not recommend substituting drugs that have not been determined to be bioequivalent. Drugs that are not listed as bioequivalent should not be substituted for each other.

❑ Objectives

- To allow review of patterns of access and usage.
- To allow discovery of use of unusual privileges.
- To allow discovery of repeated attempts to bypass protections.
- To serve as a deterrent by its existence.
- To supply an additional form of user assurance.

Content of orange book

1.	**Introduction**
1.1.	Content and Exclusion
1.2	Therapeutic Equivalence-Related Terms
1.3	Statistical Criteria for Bioequivalence
1.4	Reference Listed Drug
1.5	General Policies and Legal Status
1.6	Practitioner/User Responsibilities
1.7	Therapeutic Equivalence Evaluation Codes
1.8	Description of Special Evaluation Codes
1.9	Therapeutic Equivalence Codes Change for a Drug Entity
1.10	Change of the Therapeutic Equivalence Evaluation for a single Product
1.11	Discontinued Section
1.12	Changes to the Orange Book
1.13	Availability of the Edition

2. How to use the Drug Products Lists

2.1 Key Selection for Using the Drug Products Lists

2.2 Drug Product illustrations

2.3 Therapeutic Equivalence Evaluations illustrations

Drug Product Lists

Drug products with approval under Section 505 of the Act Administered by the center for Biologics Evaluation and Research List

Discontinued Drug Product List

Orphan Products Designations and Approvals List

Drug products which must demonstrate *in vivo* Bioavailability only if product fails to achieve Adequate dissolution

Appendices

A. Product Name Index A-1

B. Product Name Index Listed by

C. Uniform Terms

Patent and Exclusively Information Addendum

A. Patent and Exclusively Lists

B. Patent and Exclusivity Terms

Federal Register

FEDERAL REGISTER

The Daily Journal of the United States Government

- The Federal Register is the official journal of the federal government of the United States that contains government agency rules, proposed rules, and public notices. It is published every weekday, except on federal holidays.
- The final rules promulgated by a federal agency and published in the Federal Register are ultimately reorganized by topic or subject matter and codified in the Code of Federal Regulations (CFR), which is updated annually.
- The Federal Register is compiled by the Office of the Federal Register (within the National Archives and Records Administration) and is printed by the Government Publishing Office. There are no copyright restrictions on the Federal Register; as a work of the U.S. government, it is in the public domain.

History

The Federal Register system of publication was created on July 26, 1935, under the Federal Register Act. The first issue of the Federal Register was published on March 16, 1936. In 1946 the Administrative Procedure Act required agencies to publish more information related to their rulemaking documents in the Federal Register. On March 11, 2014, Rep. Darrell Issa introduced the Federal Register Modernization Act , a bill that would require the Federal Register to be published (e.g., by electronic means), rather than printed, and that documents in the Federal Register be made available for sale or distribution to the public in published form.

Code of Federal Regulations

The 50 subject matter titles contain one or more individual volumes, which are updated once each calendar year, on a staggered basis.

❖ **The annual update cycle is as follows:**

- Titles 1-16 are revised as of January 1
- Titles 17-27 are revised as of April 1
- Titles 28-41 are revised as of July 1
- Titles 42-50 are revised as of October 1

The online CFR is a joint project authorized by the publisher, the National Archives and Records Administration's (NARA) **office of the Federal Register (OFR), and the** Government Publishing Office (GPO) **to provide the public with enhanced access to Government information.**

- Each new set contains the text of all regulations in force as of the current through date. New regulations are merged with, and revoked regulations are deleted from, the previous set of regulations.
- The Office of the Federal Register also keeps an unofficial, online version of the CFR, the e-CFR, which is normally updated within two days after changes that have been published in the Federal Register become effective.
- The Parallel Table of Authorities and Rules lists rule making authority for regulations codified in the CFR.

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Title 21: Food and Drugs

Code of Federal Regulations in Pharmaceuticals

Title 21 is the portion of the Code of Federal Regulations that governs food and drugs within the United States for the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA) and the Office of National Drug Control Policy (ONDCP).

It is divided into three chapters:

- **Chapter I - Food and Drug Administration**
- **Chapter II - Drug Enforcement Administration**
- **Chapter III - Office of National Drug Control Policy**

Purple Book

- The "Purple Book" lists biological products, including any bio similar and interchangeable biological products, licensed by FDA under the Public Health Service Act (the PHS Act).
- The Purple Book includes the date a biological product was licensed under 351(a) of the PHS Act and whether FDA evaluated the biological product for reference product exclusivity under section 351(k)(7) of the PHS Act.
- It also includes whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be bio similar to or interchangeable with a reference biological product (an already- licensed FDA biological product).