Regulatory Concepts

BASIC TERMINOLOGES:

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 tiled 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 US. The data gathered during the animal studies and human clinical trials of an investigational new drug become part of the NDA. In simple words, “It is an application which is tiled with FDA to market a new Pharmaceutical for sale in USA.”

Abbreviated New Drug Application (ANDA): It is an application tiled with FDA, for a U. S. generic drug approval for an existing licensed medication or approved drug. In simple words, "It is an application for the approval of Generic Drugs.”

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 (typically, the UK's MHRA or the EMA's Committee for Medicinal Products for Human Use (CHMP) to market a drug or medicine. **As per UK's MHRA:** Applications for new active substances are described as 'full applications'. Applications for medicines containing existing active substances are described as 'abbreviated' or 'abridged applications'.

Active Substance Master File (ASMF): Active substance master file is a submission which is made to EMA, MHRA or any oth Drug Regulatory Authority in Europe to provide confidential intellectual property or 'know how' of the manufacturer of the activ substance. In simple words, “It is a submission made to European Drug regulatory agencies on the confidential information of Active Substance or Active Pharmaceutical Ingredient (API)".

International Council for Harmonization 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 designed 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 Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). CTD format for submission of drug registration applications/dossiers is widely accepted by regulatory authorities of other countries too like Canada, Australia, etc.

Orange Book: It is the commonly used name for the book "Approved Dr Products with Therapeutic Equivalence Evaluations", 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 approval of generic drugs. Paragraph IV of the act, allows 180-day exclusivity to companies that are the "first-to-file" an ANDA against holders of patents for branded counterparts.

In simple words “Hatch-Waxman act is the amendment to Federal, Food, Drug and Cosmetics act which established the modern system of approval of generics".

Patent Certifications under Hatch-Waxman Act:

As per the Hatch and 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 Filled (Para I certification).

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

(III) That the patent will expire on a particular date (Para III certification); or

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

A certification under paragraph I or II permits the ANDA to be approved immediately, if it is otherwise eligible. A certification under paragraph III indicates that the ANDA may be approved when the patent expires.

180-day 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 to defend a patent infringement suit.

180 Day Exclusivity could be granted to more than one applicant. The recent example is 180-day exclusivity was granted to Ranbaxy and Watson Laboratories for marketing generic “53% of Lipitor (Atorvastatin calcium).”

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 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 practice and the systems required to be adapted in pharmaceutical manufacturing, quality control, quality system covering the manufacture and testing of pharmaceutical or drugs including; active pharmaceutical ingredients, diagnostics, foods, pharmaceutical products and medical devices.

Good Clinical Practice (GCP): It is an international quality standard that is provided by International council for Harmonization (ICH) that defines standards, which governments can transpose into regulations for clinical trials involving human subjects.

Good Laboratory Practice (GLP): It specifically refers to a quality system of management controls for research laboratories and organizations to try to ensure the uniformity, consistency, reliability, reproducibility, quality and integrity of chemical (including pharmaceuticals) safety and efficacy tests.

Table 5.1: List of Abbreviations

Sr. No.	Abbreviation	Full Form
1.	NDA	New Drug Application
2.	ANDA	Abbreviated New Drug Application
3.	IND	Investigational New Drug Application
4.	DMF	Drug Master File
5.	ASMF	Active Substance Master File
6.	MAA	Marketing Authorisation Application
7.	CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
8.	ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
9.	CTD	Common Technical Document for the registration of pharmaceuticals for human use.
10.	RMS	Reference Member State
11.	CMS	Concerned Member State
12.	CHMP	The Committee for Medicinal Products for Human Use
13.	CPMP	Committee for Proprietary Medicinal Products
14.	cGMP	Current Good Manufacturing Practice
15.	GCP	Good Clinical Practice
16.	GLP	Good Laboratory Practice

Table 5.2: Drug Regulatory Agencies across the world

Sr. No.	Country / Region	Regulatory Agency
1.	United States of America	United States Food and Drug Administration (USFDA)
2.	United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)
3.	European Union	European Medicines Agency (EMA)
4.	China	National Medical Products Administration (NMPA)
5.	Australia	Therapeutic Goods Administration (TGA)
6.	Canada	Health Canada
7.	Japan	Pharmaceutical and Medical Devices Agency (PMDA)
8.	France	The National Agency for the Safety of Medicines and Health Products (L'Agence nationale de sécurité du médicament et des produits de santé or ANSM).
9.	Germany	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, or BfArM).

10.	Brazil	The National Health Surveillance Agency (Agência Nacional d Vigilância Sanitária or ANVISA).
11.	India	Central Drugs Standard Control Organisation (CDSCO)
12.	Switzerland	Swiss Agency for Therapeutic Products (SWISSMEDIC)
14.	Singapore	Health Sciences Authority (HSA)
15.	New Zealand	New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE)
16.	Russia	Ministry of Health of Russian Federation
17.	Ukraine	Ministry of Health of Ukraine
18.	Kazakhstan	Ministry of Healthcare of the Republic of Kazakhstan
19.	Belarus	Ministry of Health of the Republic of Belarus

Laws and Acts:

A law is written statute, requirement, ordinance passed by a legislature and signed into law by the executive (where required) at federal, state and local levels. One of the primary laws establishing the framework within which FDA operates is the Federal Food, Drug and Cosmetic Act (FD and C Act). The FD and C Act is amended by Congress from time to time. Some of the more significant amendments include the Orphan Drug Act of 1983, Food Quality Protection Act of 1996 and the FDA Food Safety Modernization Act 2011.

REGULATIONS : The FDA develops regulations based on the laws that are set forth in the FD and C Act as well as the other laws under which the FDA operates. Regulations issued by the FDA are federal laws and are modified in the Code of Federal Regulations.

When issuing regulations, the FDA follows the procedures set forth in the Administrative Procedure Act (APA). Broadly speaking, the APA sets for a Notice and Comment Rule Making process, which requires that regulatory agencies issue a proposed regulation, allow time for public input and then issue a final regulation.

Guidance and Guidelines: After a regulation is issued, the FDA may determine that it needs to provide industry, academia and other stakeholders with more information on how the FDA intends to exert (or decline to exercise, as the case may be) its regulatory authority. The FDA does this through issuing what it has termed 'Guidance' documents. The FDA follows the procedures required by its "Good Guidance Practice" regulation to issue FDA guidance. Guidance documents must not set new legal standards or impose new requirements. Unlike regulations, guidance documents do not contain amendments to the Code of Federal Regulations and are not subject to the notice and comment process.

Orange Book: Definition: It is the publication o
"Approved drug Products With Therapeutic Evaluations
by the Food and Drug Administration."

It is prepared by the orange book staff, centre 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 Cosmetic Act. The list of independent of any current regulatory action against a drug product.

Objectives:

- To 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

Contents of “THE ORANGE BOOK”:

The Orange Book is composed of four parts:
(1) approved prescription drug products with therapeutic equivalence evaluations;
(2) approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs;
(3) drug products with approval under Section 505 of the FD and C Act administered by the Center for Biologics Evaluation and Research; and
(4) a cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined that they were withdrawn from sale for safety or effectiveness reasons,

or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. This publication also includes indices of prescription and OTC drug products by proprietary name (brand name or trade name) or, if no proprietary name exists, established name of the active ingredient and by applicant name, which have been abbreviated for this publication. Established names for active ingredients generally conform to compendial names or UNITED STATES ADOPTED NAMES (USAN) as described in 21 CFR 299.4(e).

Table 5.3: Contents of "THE 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 Evaluations Codes
1.8	Description of Special Evaluations Codes
1.9	Therapeutic Equivalence Code 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

FEDERAL REGISTER: The Federal Register is a legal newspaper published every business day by the National Archives and Records Administration (NARA) of USFDA. It contains federal agency regulations; proposed rules and notices and Executive orders, proclamations and other Presidential documents. The Federal Register informs citizens of their rights and obligations and provides access to a wide range of federal benefits and Opportunities for funding. NARA's Office of the Federal Register prepares the Federal Register for publication in partnership with the Government Printing Office (GPO), which distributes it in paper and on World wide web.

CODE OF FEDERAL REGULATIONS: The Code of Federal Regulations (CFR) is the codification of the general and permanent rules and regulations (sometimes called administrative law) published in the Federal Register by the executive departments and agencies of the federal government of the United States.

The CFR is divided into 50 titles that represent broad areas subject to federal regulation. The CFR annual edition is the codification of the general and permanent rules published by the Office of the Federal Register (part of the National Archives and Records Administration) and the Government Publishing Office. The rules and regulations are first published (chronologically) in the Federal Register on a daily basis then codified in the Code of Federal Regulations. When codified, they are arranged by title, then by chapter and then by subject.

The CFR is structured into 50 subject matter titles. Agencies are assigned chapters within these titles The titles are broken down into chapters, parts, sections and paragraphs.

For example 42 CFR 260.11(a)(1) would be read as "title 42, part 260, section 11, paragraph (a)(1)."

While new regulations are continually becoming effective, the printed volumes of the CFR are issued once each calendar year, on this schedule:

Titles 1-16 are updated as of January 1.

Titles 17-27 are updated as of April 1.

Titles 28-41 are updated as of July 1.

Titles 42-50 are updated as of October 1.

The Office of the Federal Register also keeps an unofficial, online version of the CPR, the e-CFR, which is normally updated within two days after changes that have been published in the Federal Register become effective.

CFR Title 21 also known as 21 CFR is the Title/ Section concerned with the rules and regulations of the pharmaceutical sector.

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.

In all, Title 21 of CFR consists of 1499 articles, all of which pertain to various aspects associated with the pharmaceutical sector.

A revised Title 21 is issued on approximately April 1st of each year.

PURPLE BOOK: The "Purple Book" lists biological products, including any biosimilar 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 biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product).