1.*What is Regulatory Affairs?*

Ans-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.

2.*What are the goals of Regulatory Affairs Professionals?*

Ans-

- Protection of human health
- Ensuring safety, efficacy and quality of drugs
- Ensuring appropriateness and accuracy of product information

3.*What are the Roles of Regulatory Affairs professionals?*

Ans-

- Act as a liaison with regulatory agencies
- Preparation of organized and scientifically valid NDA, ANDA,INDA ,MAA,DMF submissions
- Ensure adherence and compliance with all the applicable cGMP, ICH, GCP, GLP guidelines, regulations and laws
- Providing expertise and regulatory intelligence in translating regulatory requirements into practical workable plans
- Advising the companies on regulatory aspects and climate that would affect their proposed activities
- Apart from the above main roles, there are various other roles which Regulatory Affairs professionals play.

4.*What is an Investigational New Drug (IND) application?*

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

5.*What is a New Drug Application?*

Ans- 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

In simple words, "It is an application which is filed with FDA to market a new Pharmaceutical for sale in USA"

6.*What is an Abbreviated New Drug Application (ANDA)?*

Ans- It is an application filed 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 "

7.*What is a Generic Drug Product?*

Ans- 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.

8.*What is a DMF?*

Ans- 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.

Important facts regarding DMFs

- It is submitted to FDA to provide confidential information
- Its submission is not required by law or regulations
- **It is neither approved nor disapproved**
- It is filed with FDA to support NDA, IND, ANDA another DMF or amendments and supplements to any of these
- It is provided for in the 21 CFR (Code of Federal Regulations) 314. 420
- It is not required when applicant references its own information

9.*What are the types of DMF's?*

Ans-

Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel (No longer accepted by FDA)

Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

Type III: Packaging Material

Type IV : Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

Type V: FDA Accepted Reference Information (FDA discourages its use)

10.*What is a 505 (b)(2) application ?*

Ans- 505 (b)(2) application is a type of NDA for which one or more investigations relied on by applicant for approval were not conducted by/for applicant and for which applicant has not obtained a right of reference.

11.*What kind of application can be submitted as a 505(b)(2) application?*

Ans-

- New chemical entity (NCE)/new molecular entity (NME)
- Changes to previously approved drugs

12. *What are the examples of changes to approved drug products for which 505(b)(2) application should be submitted ?*

Ans-

- Change in dosage form.
- Change in strength
- Change in route of administration
- Substitution of an active ingredient in a formulation product
- Change in formulation
- Change in dosing regimen
- Change in active ingredient
- New combination Product
- New indication
- Change from prescription indication to OTC indication

- Naturally derived or recombinant active ingredient
- Bioinequivalence

13.*What are the chemical classification codes for NDA?*

Ans-

Number	Meaning
1	New molecular entity (NME)
2	New ester, new salt, or other noncovalent derivative
3	New formulation
4	New combination
5	New manufacturer
6	New indication
7	Drug already marketed, but without an approved NDA
8	OTC (over-the-counter) switch

14.*What are the differences between NDA and 505 (b)(2) application ?*

Ans-

S.No.	New Drug Application (NDA)	505 (b)(2) Application
1.	All investigations relied on by applicant for approval were conducted by/for applicant and for which applicant has right of reference	One or more investigation relied on by applicant for approval were not conducted by/for applicant and for which applicant has not obtained a right of reference
2.	Generally, filed for newly invented pharmaceuticals.	Generally, filed for new dosage form, new route of administration, new indication etc for all already approved pharmaceutical.

Note: 505 (b)(2) application is a type of NDA.

15.*What is a Marketing Authorization Application?*

Ans- 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'.

16.*What is an ASMF?*

Ans-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.

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)".

17.*What are the types of active substances for which ASMFs are submitted?*

Ans-

- New active substances
- Existing active substances not included in the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member State
- Pharmacopeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State

18.*What is the difference between DMF and ASMF (with respect to submission)?*

Ans-ASMF is submitted as Applicant's Part (Open Part) and Restricted Part (Closed Part)

There isn't any differentiation of DMF's into parts

19.What is ICH?

Ans-International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): 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.

20.*What is CTD?*

Ans-The Common Technical Document (CTD) 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 Conference on Harmonisation of Technical Requirements for Registration of 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.

21.*What are the ICH guidelines to be referred for preparation of registration dossiers/applications of medicines (With respect to format and contents in each module)?*

Ans-

M4 Guideline

M4Q Guideline

M4S Guideline

M4E Guideline

22.*What are the modules in CTD?*

Ans-

The Common Technical Document is divided into five modules:

Module 1. Administrative information and prescribing information

Module 2. Common Technical Document summaries (Overview and summary of modules 3 to 5)

Module 3. Quality

Module 4. Nonclinical Study Reports (toxicology studies)

Module 5. Clinical Study Reports (clinical studies)

22.*What is Orange Book?*

Ans-

- It is the commonly used name for the book "**Approved Drug 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.

23.*What is Hatch-Waxman act?*

Ans-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 "

24.What are the patent certifications under Hatch-Waxman act?

Ans-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 filed (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.

25.*What is meant by 180 day exclusivity?*

Ans-The Hatch-Waxman Amendments provide an incentive of 180 days of market exclusivity to the "first" generic applicant who challenges a listed patent by filing 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 version of Lipitor (Atorvastatin calcium).

26.*What are the procedures for Approval of Drug in EU?*

Centralised Procedure (CP)

Decentralised Procedure (DCP)

Mutual Recognition Procedure (MRP)

National Procedure (NP)

27.*What is the Full form of abbreviation, CEP?*

Certificate of Suitability to the monographs of the European Pharmacopoeia (or) Certificate of suitability of monographs of the European Pharmacopoeia (or) Certification of suitability of European Pharmacopoeia monographs

It is also informally referred to as Certificate of Suitability (COS)

28.*What is a 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.

29.*What are the recently approved new Drugs by FDA (Under NDA Chemical Type 1)? (As on 14th March, 2012)*

Ans-

S.NO.	NDA #	NAME OF DRUG	NAME OF ACTIVE INGREDIENT	COMPANY
1	203188	KALYDECO	IVACAFTOR	VERTEX PHARMS
2	203388	ERIVEDGE	VISMODEGIB	GENENTECH
3	202324	INLYTA	AXITINIB	PFIZER
4	202833	PICATO	INGENOL MEBUTATE	LEO PHARMA AS
5	202514	ZIOPTAN	TAFLUPROST	MERCK SHARP DOHME
6	021746	SURFAXIN	LUCINACTANT	DISCOVERY LABORATORIES INC

30.*Full forms of some of the Abbreviations related to Regulatory Affairs-*

S.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 Conference on Harmonisation of technical requirements for registration of Pharmaceuticals for human use.
9	CTD	Common technical document for the registration of pharmaceuticals for human use.
10	AP	Applicant's Part
11	RP	Restricted Part
12	OP	Open Part
13	CP	Closed Part
14	NME	New Molecular Entity
15	NCE	New Chemical Entity
16	SmPC	Summary of Product Characteristics
17	PL	Packaging Leaflet
18	RMS	Reference Member State
19	CMS	Concerned Member State
20	CHMP	The Committee for Medicinal Products for Human Use
21	CPMP	Committee for Proprietary Medicinal Products
22	CVMP	Committee For Medicinal Products For Veterinary Use
23	SUPAC	Scale-up and post approval changes
24	BACPAC	Bulk Active Chemicals Post approval Changes
25	cGMP	Current good Manufacturing Practice
26	GCP	Good clinical Practice
27	GLP	Good Laboratory Practice

31.*Well known Drug Regulatory Agencies across the world-*

S.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	European Union	European Directorate for the Quality of Medicines **(EDQM)**
5	Australia	Therapeutic Goods Administration **(TGA)**
6	Canada	Therapeutic Products Directorate **(TPD)** in Health Product and food branch **(HPFB)** of Health Canada **(HC)**
7	Japan	Pharmaceutical and Medical Devices Agency **(PMDA)**
8	France	Agence Francaise de Securite Sanitaire des Produits de Sante **(AFSSAPS)** Translated into English as- French Agency for the Safety of Health Products
9	Germany	Bundesinstitut für Arzneimittel und Medizinprodukte, (**BfArM**) Tanslated into English as- Federal Institute for Drugs and Medical Devices
10	Brazil	Agência Nacional de Vigilância Sanitária **(ANVISA)** Tanslated into English as- The National Health Surveillance Agency
11	India	Drugs Controller General of India **(DCGI)** who heads 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)**

Effective Dossier Management in Regulatory Affairs

Importance of effective dossier management-

- The registration dossier for medicines is an important document which is submitted for review to regulatory agencies by pharma companies for approval to market their medicines.

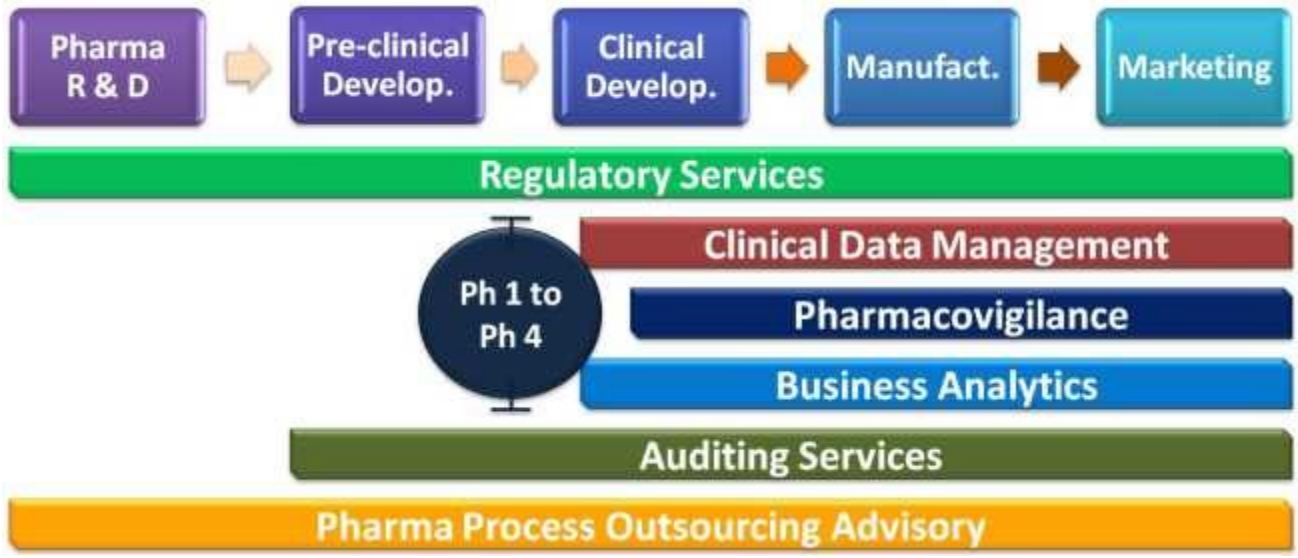
- Utmost care should be taken during its compilation and filing as it plays a direct role in earliest possible availability of medicines in the market which in turn translates into business for the company.

- Of course, regulatory affairs professionals need to ensure the safety, quality and efficacy of the medicines for which they are filing registration dossier.

Note : The dossiers could be anything among DMF, ASMF, ANDA, NDA or MAA.

From my experience I could possibly think of 3 important aspects which play an important role in effective dossier management-

1. Planning aspects
2. Formatting and compilation aspects
3. Review aspects



1. Planning aspects-

- **Deadline**-It is important to know the deadline for filing the dossier and action plan should be prepared so as to meet the deadline.

- **Understanding the registration requirements of respective agencies-** Although most of the regulatory agencies accept the CTD format for registration dossier, the requirements for approving marketing applications may vary for individual agencies. For example- USFDA requires Batch Manufacturing Records to be provided, while it is not necessary for approval by European regulatory agencies. Hence it is necessary to completely read and understand the guidance document of each regulatory agency before going ahead with filing registration dossier with them.

- **Requirements Listing**- Listing down all the requirements for preparing the registration dossier, for example in the preparation of section 3.2.S.1 of a DMF I need to have all the information on nomenclature, structure and general properties (like pH, Pka, solubility, partition coefficient, stereochemistry etc) of drug substance. Similarly Listing down all the requirements for preparation of all the modules and their respective sections is an important aspect.

- **Sending the requirements list to respective departments**-Preparing an individual requirement list and sending them to each respective department. For example I need to have all the information regarding the general properties, synthetic scheme, manufacturing process development of drug from R & D department and finalised specification & test procedures, Batch manufacturing sheets from Quality assurance department.

2. Formatting and Compilation Aspects-

Format-

As per the ICH's M4 guideline the following are recommended-

- The display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents.

- Text and tables should be prepared using margins that allow the document to be printed on both A4 and 8.5 x 11" paper (For Europe and Japan regions A4 paper is recommended and 8.5 x 11" paper for USA).

- Times New Roman, 12-point font is recommended for narrative text.

- The left-hand margin should be sufficiently large that information is not obscured by the method of binding.

- Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying.

- Every page should be numbered, according to the granularity document (refer pages 6 to 14 of M4 guideline).

- Acronyms and abbreviations should be defined the first time they are used in each module.

- References should be cited in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE).

- All pages of a document should include a unique header or footer that briefly identifies its subject matter.

Note: For any person who is new/relatively new to the field of RA it is important to read and understand CTD guidelines of ICH (M4, M4Q,M4S, M4E) before starting to compile any dossier. (Refer the post CTD in my blog)

Compilation-

The following compilation aspects are important-

- The information should be specific, clear, precise and accurate.
- Typographical and grammatical errors should be avoided.
- The information should be arranged in a sequential order in computer. Each module could have a separate folder and in turn each section of a module could have a separate folder. This kind of orderly arrangement will help in easy access of information and help in taking printouts of finalized copy conveniently.
- The line spacing should be preferably single.
- All the documents received from other departments should be cross-checked so as to ensure that they are free from errors.
- Ensuring the specifications & test procedures are designed in accordance with ICH guidelines Q3A, Q3B, Q3C, Q6A and Q6B. Stability Protocols are designed as per ICH guidelines Q1A through Q1E . Similarly ensuring that various documents are designed as per ICH guidelines. This can be ensured during drafting stages of preparation of various documents.
- After the finalized soft copy is ready, printouts should be taken using a good quality printer and arranged sequentially in a module and section wise manner.
- As per the note given in the website of EMA-"All Microsoft Office documents submitted to the European Medicines Agency must be in a format compatible with MS Office 2003. Office 2007 and Office 2010 formats cannot currently be accepted".

3.Review Aspects

- .Every human being is prone to make mistakes; hence it is important to **re check** the information in the dossier before filing it with regulatory agencies.
- It is also important that a dossier meant to be filed with a regulatory agency should be **cross verified** by a person other than the one who has complied the dossier.
- It is very useful to have a **check list** so as to ensure that all the required information is present in the dossier before submission to regulatory agency.
- The USFDA has a check list which is very useful while filing an ANDA- ANDA checklist

- The module 1 of CTD in most of the cases is completely different for various agencies hence care should be taken in compiling this section.

Avoiding Deficiencies-

You can learn without necessarily making mistakes. EDQM has compiled a list of top 10 deficiencies of CEP dossier which will go a long way in preventing you from making the same mistakes.

Key software skills for effective dossier management-

- Proficiency in **MS office** (Yes, I know that most of you are proficient!).
- Proficiency in **Adobe Acrobat tools**. (Especially useful in preparing NeeS dossier and eCTD).
- Proficiency in **ISIS draw** or **Chem sketch** softwares, which are useful in drawing chemical structures.
- Since we generally receive number of mails on a daily basis, we could sort the emails by using labels based on the sources. This will make your job easy while accessing mails.
- eCTD is mandatory for the centralised procedures in Europe and it could be made mandatory for the other procedures as well in the future. Hence it is important to undergo training in the use of **eCTD software**.(My fellow Indian countrymen, let me know if there are any institutes which are offering training in the use of eCTD software back here in India)