

BP 702 T. INDUSTRIAL PHARMACY II

Industrial Pharmacy (II) – Unit III

By

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Regulatory affairs - Regulatory Affairs (RA), also called Government Affairs, is a profession developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, foods, cosmetics and complementary medicines etc.

As a discipline, regulatory affairs cover a broad range of specific skills and occupations. Under the best of circumstances, it is composed of a group of people who act as a liaison between the government, industry, and consumers to make sure that marketed products are safe and effective when used as it advertised.

People who work in regulatory affairs negotiate the interaction between the regulators (the government), the regulated (industry), and the market (consumers) to get good products to the market and to keep them there while preventing bad products from being sold.

Pharmaceutical Drug Regulatory Affairs (DRA) is a dynamic field that includes scientific, legal and commercial aspect of drug-development.

Drug development to commercialization is highly regulated. Every drug before getting market approval must undergo rigorous scrutiny and clinical trials to ensure its safety, efficacy and quality. These standards are set by regulatory authorities of their respective countries such as FDA in US and CDSCO in India etc.

Regulation of Drug products involve following areas –

- Non-clinical and Clinical Drug Development Guidelines
- Licensing (Patent)
- Drug Registration
- Manufacturing
- Quality and safety Guidance
- Pricing and Trademark
- Marketing, Import and Distribution of Drug products
- Pharmacovigilance (Adverse Drug Reactions monitoring)

Table 1 - Historical Overview of RA (Key regulatory events with year)

Year	Event	Purpose
1906	Pure Food and Drug Act	Prevent false claims
1930	FDA takes its current name	Agency is purely regulatory—no research functions
1938	Federal Food, Drug, and Cosmetic Act	Require proof of safety before marketing
1949	First publication of FDA “Guidance to Industry”	Address the appraisal of toxic chemicals in foods
1962	Kefauver–Harris Drug Amendments	Require proof of efficacy and safety before marketing
1987	Prescription Drug Marketing Act	Ensure that pharmaceutical products purchased by consumers are safe and effective, and free from counterfeit, adulterated, misbranded, subpotent, or expired drugs
2004	Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach	Emphasize risk-based approaches to development and manufacturing
2004	PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance	Achieve greater understanding of drug development and manufacturing processes. Data acquisition and multivariate analysis cited as important tools
2005	ICH Harmonized Tripartite Guideline: Pharmaceutical Development, Q8	Foster quality by design and the understanding of design space—emphasis on design of experiments to define interactions and work in multidimensions
2005	ICH Harmonized Tripartite Guideline: Quality Risk Management, Q9	Encourage the use of quality risk-management tools in all phases of a product’s lifecycle
2007	ICH Harmonized Tripartite Guideline: Pharmaceutical Quality System, Q10	Enhance science- and risk-based regulatory approaches

Regulatory Authorities -

Public health being the prime concern, it is necessary that the drug/drug product available for human/veterinary use and medical devices must not only be effective but also be safe for the intended use. To ensure this, various territorial regulatory bodies came into existence.

Major regulatory agencies include World Health Organization (WHO), United States Food and Drug Administration (USFDA, United States), European Medicines Agency (EMA, European Union), Medicines and Healthcare Products Regulatory Agency (MHRA, UK), Therapeutic Goods Administration (TGA, Australia), Health Canada (Canada), Pharmaceuticals and Medical Devices Agency (PMDA, Japan) and Central Drugs Standard Control Organization (CDSCO, India).

It was observed that regulatory guidelines differ with respect to territorial requirements; this demanded the need for universal harmonisation. Thus, **The International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)** was founded in 1990 by united efforts of the United States, Europe and Japan to bring together different regulatory bodies globally and set ICH Guidelines for pharmaceutical drug product development. Since its inception, the ICH has evolved gradually with a mission to attain better harmonisation towards development and registration of medicines with a higher degree of safety, efficacy and quality worldwide. Although ICH has harmonised the drug regulatory aspects worldwide, the regional regulatory bodies continue to play a pivotal role in drug approvals across the territory.

Role of Drug Regulatory Affairs Department:**A) In Development phase -**

- Ensuring that the legislative requirements are met -

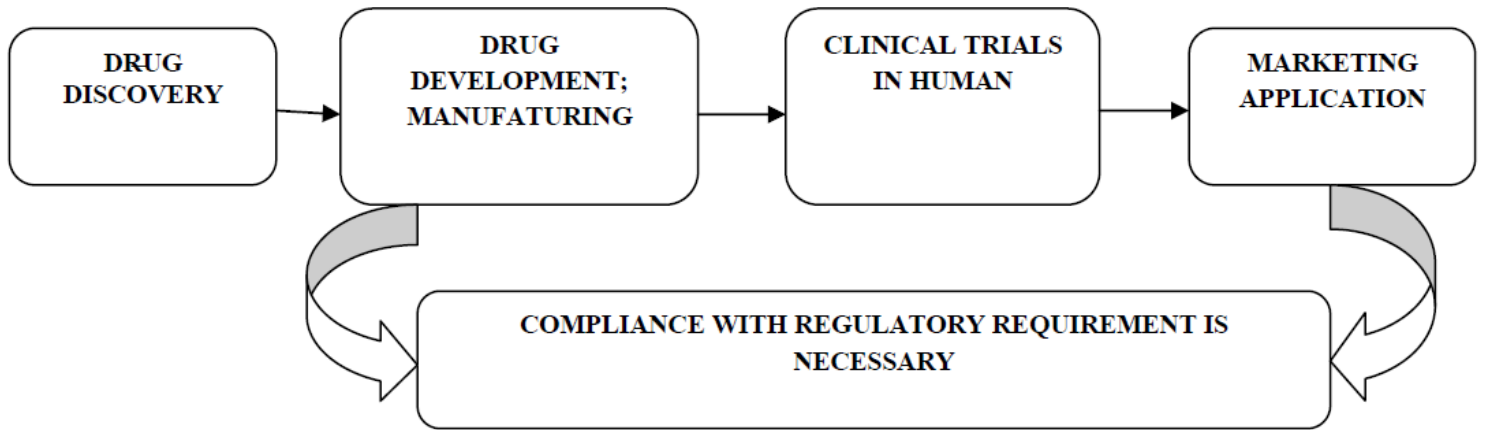


FIGURE 1: Regulation of drug approval process

Recruit Scientific Advice - authorities

– Advice on development studies to demonstrate safety, quality and efficacy parameters.

- Set up regulatory strategy.
- Participate in cross-functional project teams.
- Ensure application of guidelines for clinical trials.
- Submission of application to conduct clinical trials.
- Managing the regulatory submission -
 - Minimize time to market (every day counts!)
 - Advice on a global development plan
- Optimize submission strategies -
 - Dossier preparation
 - Format, document re-uses
 - Electronic submissions
 - Review high-level documents/reports
- Interact with commercial side of business such as pricing and reimbursement.

B) In approval phase -

- Check progress of evaluation and anticipate questions.
- Clarify raised questions, plan response and strategies with other departments.
- Plan and manage agency meetings/hearings.
- Negotiate approval and Product Information with agencies.

C) In post approval phase -

- Compliance
- Submission of variations/amendments
- Renewals
- Pharmacovigilance

- Product information review
- New indications / new formulations
- Regulatory input to development plans/ Regulatory Intelligence.

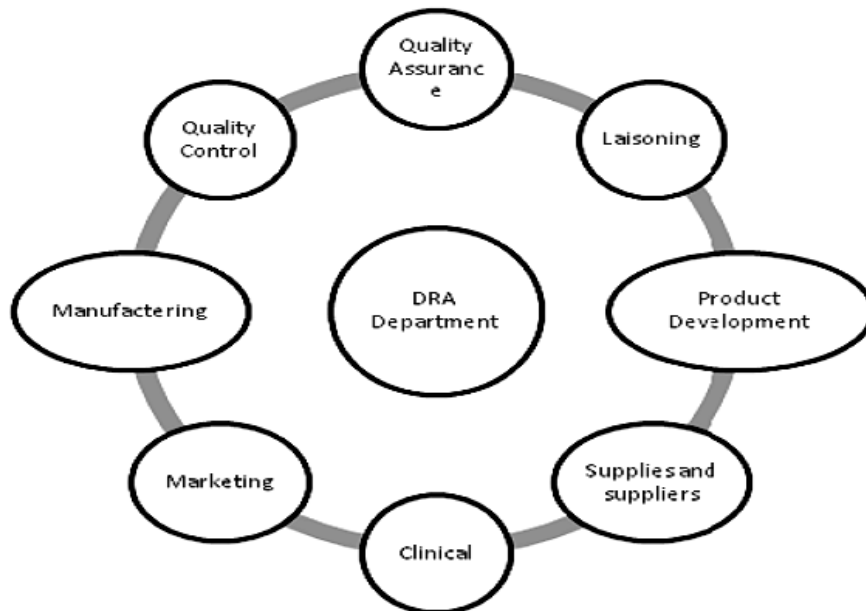


Figure 2 – Various Role of Drug Regulatory Affairs Department

Responsibility of the Regulatory Affairs Professionals -

- Ø Ensuring that their companies comply with all of the regulations and laws pertaining to their business.
- Ø Working with federal, state and local regulatory agencies and personnel on specific issues related to their business.
- Ø Advising companies on the regulatory aspects and climate that would affect their proposed activities.
- Ø Keep in touch with international legislation, guidelines and customer practices.
- Ø Keep up to the date with a company's product range.
- Ø Collect, collate, and evaluate the scientific data that their research and development colleagues are generating.
- Ø Formulate regulatory strategies for all appropriate regulatory submissions such as domestic, international and/or contract projects.
- Ø Coordinate, prepare and review all appropriate documents for example dossier and submit them to regulatory authorities within a specified time frame in conjugation with the organization.
- Ø Prepare and review of SOPs related to RA. Review of BMR, MFR, change control and other relevant documents.
- Ø Monitor the progress of all registration submission.
- Ø Maintain approved applications and the record of registration fees paid against submission of DMF's and

other documents.

Ø Respond to queries and ensure that registration/ approval are granted without delay.

Ø Participate in R&D training, Pilot plant Scale Up, and Post Marketing Surveillance (ADR).

Ø Manage and review audit reports and compliance, regulatory and customer inspections.

Ø Provide accurate and complete information about the quality, safety and effectiveness of the product to the physicians and other healthcare professionals.

Regulatory requirements for drug approval:

Drug Development Teams - Most pharmaceutical and biotechnology firms employ drug development project teams to guide the processes involved in early drug discovery phase, through the various drug development stages and finally making the drug candidate into a therapeutic product.

The drug development team includes a diverse group of individuals with different philosophies and approaches to the development process. All team members must work closely together to ensure that a drug is both safe and efficacious.

The responsibilities of these project teams include -

1. Reviewing research results from experiments conducted by any of the various scientific disciplines.
2. Integrating new research results with previously generated data.
3. Planning research studies to further characterize a drug candidate.
4. Preparing a detailed drug development plan, including designation of key points or development milestones, generating a timeline for completion, and defining the critical path.
5. Monitoring the status of research studies to ensure that they are being conducted according to the timeline and critical path in the development plan and, if appropriate, modifying the plan as new information becomes available.
6. Comparing research results and development status and timelines with drug candidates under development by competitors.
7. Conducting appropriate market surveys to ensure that the development of a drug candidate is economically justified and continues to meet a medical need.
8. Reporting the status of the drug development program to management and making recommendations on the continued development of the drug candidate.

Drug development teams consist of following group of teams -

1. Discovery/development Team

The discovery and development groups are comprised of the basic scientists and chemists who created the new molecule. This group synthesizes drug substances for “drug-screening,” pharmacology, and toxicology studies, and also prepares clinical supplies.

2. Nonclinical pharmacology and toxicology Team

This group studies the drug product in animal models for efficacy and safety in order to identify potential efficacy and safety issues in humans. It is critical for the clinical and development groups to work closely with the toxicologists in the design of animal studies to ensure their relevance to the clinical environment.

3. Clinical research Team

Clinical research has the ultimate responsibility for testing drug products in humans: the monitoring of drug safety rests squarely on the shoulders of clinical research. Clinical trials must be science-based with proper statistical methodologies and have clinically relevant end points. Clinical research interacts directly with the FDA and is responsible for the generation of study reports with input from biostatisticians and regulatory affairs. Clinical research can also generate the publications necessary for the marketing of any drug product.

4. Regulatory affairs Team

The regulatory affairs department is the interface with the FDA. It is their responsibility to ensure compliance with the rules and regulations established by the Federal Food Drug and Cosmetic Act and its amendments.

5. Marketing Team

The marketing group has the ultimate responsibility for marketing and selling the drug. As a result, they need product, labeling that differentiates their drug from those already marketed. Marketing has to provide creative concepts for the prescribing physician, the patient, and the company's senior management. They also have to make sure that budget goals are met. It is not uncommon for the marketing group to have differences of opinion from both the clinical and regulatory groups within their own company, as well as with the FDA.

6. Legal Team

In order for a drug to be financially successful, patent protection is a key element. The legal group must submit patents at the appropriate time and do all in its power to avoid lawsuits from potential competitors. The legal group also ensures that neither the FDA nor the other organization or company will challenge advertising and promotional materials.

7. Management Team – They co-ordinate with all the respective teams and responsible for successful completion of project in a time bound manner.

Pharmaceutical Drug Development:

- Pharmaceutical Drug Development is a process of bringing a newly synthesized drug molecule to the market once a lead compound has been identified through the process of drug discovery.

- These newly synthesized drug molecules which also known as New chemical entities (NCEs) or as New molecular entities (NMEs) are identified as Lead compound if they show promising pharmacological activity against a particular biological target that play a major role for a particular disease.

- The Identification of lead compound is carried out in drug discovery phase by means of suitable screening techniques such as High-throughput Screening.

- Drug Development process consist of a number of events that took place between the discovery of Lead compound to its eventual marketing.

- Broadly, the process of drug development can be divided into pre-clinical/non clinical and clinical phases.

- **Pre-clinical or Non- clinical Phase of Drug Development:** Pre-clinical Drug Development involves pharmacological and toxicological assessment of the potential new drug in animal models in order to establish its safety and efficacy before the administration to human volunteers in clinical trial phase.

- Pharmacological and toxicological assessment of the potential drug candidate is carried out by both in-vitro and in-vivo methods and in accordance with the guidelines of good laboratory practice (GLP). The GLP regulations are found in - 21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies.

- Cell lines or isolated tissues are used as in-vitro models and both rodent and non rodent animals such as mice, rat, guinea pig, dog, monkey etc are used as animal models for in-vivo testing.

- Such preclinical studies can be take up to 2 years to complete.

O Pre-clinical Drug Development involves following major type of studies –

1. Pharmacological studies -

i) Pharmacokinetic profile Study – It deals with study of ADME. Generally, ADME studies are conducted in two species, usually rats and dogs, repeated with different dose levels in males & females.

The main task of pharmacokinetic studies is to find an optimal dose level and to provide information about the dose-effect relationship. Therefore, different processes in the body are investigated and intensive information about the absorption, distribution, metabolism and excretion (ADME) of the substance is generated.

<i>In vitro</i>	<i>In vivo</i>	<i>In vivo</i>
1) Physical/chemical properties [lipophilicity (log P/log D), solubility, chemical stability (pKa)]	1) Pharmacokinetic profile (concentration versus time) - Area under the curve	1) Toxicokinetic - Pharmacokinetic profile (concentration versus time)
2) Metabolic stability	- C _{max}	- Area under the curve
3) Hepatic clearance	- T _{max}	- C _{max}
4) Interaction between substances (inhibition/induction of CYPs)	- Distribution	- T _{max}
5) Physiological characteristics (plasma protein/tissue binding)	- Clearance	- Distribution
6) Permeability	- Half-life time	- Clearance
7) Plasmatic stability and total blood/plasma partition	2) Biodisponibility bioavailability	- Half-life time
	3) Linearity	2) Biodisponibility
	4) Metabolization	3) Metabolization
	5) Routes of excretion	4) Routes of excretion
		5) Quantification of biological fluids, organs, tissues, excrements and expired air (when necessary)

Table 2- Recommended non-clinical assays of ADME/PK.

●**Metabolism Study:** The drug metabolism studies needed to characterize the fate (whether the compound is changed and to what) of a lead or drug candidate in the body. Metabolism studies carried out by both *in-vitro* and *in-vivo* methods.

The *in-vitro* experiments can be conducted in a variety of systems, including CYP450 isozymes (the enzymes responsible for most oxidative metabolism of drugs), microsomes, hepatocytes, or liver slices. Since hepatocytes contain both phase 1(oxidative, hydrolysis, and reduction) and phase 2 (conjugation) metabolism systems and can be relatively easily obtained from pharmacology and toxicology animal species and from humans, many researchers select this model for the first assessment of metabolism. If the results from hepatocytes show extensive metabolism, additional *in-vitro* experiments are usually conducted first in microsomes to ascertain if oxidative metabolism is present and then in isolated CYP450 isozymes to determine which enzyme or enzymes are responsible.

For *in-vivo* metabolism studies in animal models, the selected animal species have metabolism profile that is similar to humans. Drug metabolism experiments in animal species used or to be used in toxicology studies are conducted using an appropriately labeled compound, usually a radioactive isotope such as carbon-14. Sometimes, drug metabolism studies are conducted with a less than desirable radiolabel isotope, such as 125I or 3H.

For more reliable results, the radiolabeled compound should be radiochemically pure and stable and have a specific activity high enough to be measurable after dosing. Also, the label needs to be in a position where it

does not affect the physical, chemical, or pharmacological properties of the candidate and is not lost during phase 1 (oxidation, reduction, cleavage) or phase 2 (conjugation) metabolism.

The total radioactivity minus the parent compound concentration (determined by the bioanalytical assay method) in a specimen (plasma, serum, urine, bile), estimates the amount of metabolites present. If the difference is minimal and does not change over time, the extent of metabolism is low. For plasma or serum specimens, a small difference indicates that metabolites are not present in systemic circulation. For bile or urine specimens, high levels of radioactivity suggest a primary route of elimination for the parent and metabolites. Study of metabolite profile in urine and bile carried out to determine the amount of each potential metabolite. When the level of a metabolite is high, i.e., greater than 5% of the parent compound, attempts to isolate and identify the metabolite should be undertaken and metabolite's pharmacological and toxicological activity are evaluated.

ii) Pharmacodynamic profile Study – Pharmacodynamic studies deal more specifically with followings-

a) Primary pharmacodynamic (PD) study - Study Physiological effects of drug

b) Secondary pharmacodynamic study - Study Mechanism of drug action and effects of the relevant compound which are not related to its desired therapeutic target.

c) Safety pharmacology studies - Safety pharmacology studies are conducted to identify possible undesirable pharmacodynamic effects of a compound on selected physiological functions which may have an impact on human safety. Three types of safety pharmacology studies are performed which are as follows:

● **Core battery study** - The core battery of safety pharmacology studies which should be conducted in accordance with GLP is mandatory in order to investigate before first administration in humans. The core battery implies organ systems which are important with respect to life-supporting functions and are therefore most critical for life. This includes the cardiovascular, respiratory and central nervous system. Thereby, in vitro studies on isolated tissue, cells, receptors, ion channels or enzymes are an initial method to investigate potential pharmacological effects in concentration ranges of the respective substance on which an effect seems probable. For subsequent in vivo studies, the expected clinical route of administration should be used and the animals should ideally not be under anesthesia.

Safety pharmacology studies are normally performed by a single dose administration, whereby the exposure should at least be similar or even higher than the potential therapeutic concentration in humans.

b) Follow-up studies - The follow-up studies for the core battery may provide a deeper insight into kinetic conditions and potential repeat dose administrations on a suitable animal species.

c) Supplemental studies - In supplemental safety pharmacology studies organ systems not addressed in the core battery are investigated. This is notably done with other major organ systems such as the gastrointestinal, renal or the immune system.

2. Toxicological Studies - Toxicology defines the preclinical part of the safety assessment during drug development. By conducting toxicity studies, possible hazards and risks are identified.

i) Acute toxicity (Single dose) and Chronic toxicity (Repeated-dose) study –

- Acute toxicity is usually assessed by administration of a single high dose of the test drug to rodents. Both rat and mice (male and female) are usually employed.
- The single dose is administered by at least two routes, one of which should be the proposed route to be used in human beings. Animals are observed for overt effects and mortality up to 2 weeks and LD50 value is determined at 95% confidence level.
- **Repeated-dose** toxicity studies should be carried out in at least two species, out of which one should be a non-rodent. For **Repeated-dose** toxicity study small doses of drug administered 7 days a week up to 6 – 9 months.
- At least three dose levels should be used; the highest dose should produce observable toxicity, the lowest dose should not produce observable toxicity, but should be comparable to the intended therapeutic dose in humans; the intermediate dose should produce some symptoms, but not gross toxicity or death, and may be placed logarithmically between the other two doses. Observations should include body weights, clinical signs, clinical chemistries, hematology, and detailed histopathological changes in cells and tissues that occurred due to toxicity.

ii) Reproductive toxicity study – These studies evaluate male and female fertility, embryo and fetal death, parturition and the newborn, the lactation process, care of the young, and the potential teratogenicity of the drug candidate.

Historically, these reproductive parameters have been evaluated in three types of studies, generally referred to as **segment I, segment II, and segment III**.

Segment I, evaluates fertility and general reproductive performance in rats.

Segment II, commonly conducted in rats and rabbits, determines the embryo toxicity or teratogenic effects of the drug candidate.

Segment III, designated the perinatal and postnatal study and normally conducted only in rats, assesses the effects of the drug candidate on late fetal development, labor and delivery, lactation, neonatal viability, and growth of the newborn.

Other rodents and nonrodent species, such as mice, guinea pigs, mini pigs, ferrets, hamsters, dogs, and nonhuman primates, have been used to evaluate the reproductive toxicity of drug candidates.

In Segment I, male fertility is determined by pre-mating dosing of at least 4 weeks and with dosing continuing throughout the mating period. Histopathology of these tests and sperm analysis is used to

detect effects on spermatogenesis. Female fertility is determined by pre-mating dosing of at least 14 days with dosing continuing during the mating period.

Segment II, or Teratology studies, are designed to ascertain if a drug candidate has potential for embryotoxicity or teratogenic effects and are conducted in a rodent and nonrodent species. The drug candidate is administered during the period of organogenesis, which is usually considered gestation day 6 to 15 for mice and rats and gestation day 6 to 18 for rabbits. Fetuses are delivered by Cesarean section a day or two before anticipated parturition. For rats, half of the fetuses are examined for visceral alterations and the other half are evaluated for skeletal abnormalities. For rabbits, microdissection techniques for soft tissue alterations allow all of the fetuses to be examined for both soft tissue and skeletal abnormalities.

Segment III studies are usually conducted only in rats and are designed to evaluate effects on perinatal and postnatal development of pups and on maternal function. The drug candidate is administered to the dams from implantation to the end of lactation. At the time of weaning, normally one male and one female offspring per litter are selected for rearing to adulthood and mating to assess reproductive competence.

iii) Genotoxicity / Mutagenicity Study – Mutagenicity study aim to determine whether the proposed drug is capable of inducing DNA damage, either by inducing alterations in chromosomal structure or by promoting changes in nucleotide base sequence. Mutagenicity studies are usually carried out by both in vitro and in vivo methods. The standard battery of tests recommended by ICH consists of a gene mutation assay in bacteria, an in vitro test of chromosomal damage, or an in vitro mouse lymphoma thymidine kinase (TK) assay, and an in vivo test of chromosomal damage using rodent hematopoietic cells.

Genetic toxicology test	Purpose
Ames bacterial mutation assay	Gene mutation in bacteria
Mouse lymphoma assay (MLA) Chinese hamster ovary (CHO) chromosomal aberration assay	In vitro evaluation of chromosomal damage
Micronucleus test (MNT)	Evaluation of in vivo chromosomal damage in bone marrow polychromatic erythrocytes

Table 3- Standard Genetic Toxicology Test Battery (ICH)

iv) Carcinogenicity Study – Long-term carcinogenicity study is carried out, particularly if the drug is used for administration over prolonged period (≥ 6 months). In such type of study animal is observed for the development of tumors.

Carcinogenicity studies are conducted in two rodent species (mostly rats and mice) over a long-term period of 2 years. Two types of dose is used for the study – 1. Maximum tolerated dose (MTD) and 2. 25-fold AUC ratio (25:1 exposure ratio of rodent to human plasma AUC of the parent compound)

v) Immunotoxicity Study – Ability of the drug compound to induce immune response or sensitivity is studied. Immunotoxicity which may be investigated during repeated dose toxicity studies. It identifies adverse

effects of drugs on the immune system as immunosuppression which can lead to infectious diseases or malignancies, hypersensitivity or autoimmune reactions to self antigens. To determine potential immune reactions, different parameters like antibodies (IgM, IgE, IgG, etc.) are quantified, lymph nodes are weighed or lymphoid cell morphology is analyzed.

vi) Toxicokinetic Studies – Toxicokinetic studies may be an integral part of nonclinical toxicity studies or may be conducted as separate, supportive studies. In general, toxicokinetic studies should be performed according to GLP regulations in conjunction with drug safety studies.

The primary objective of toxicokinetics studies is to define systemic exposure in animals along with the relationship of such exposure to the dose level and time course of the toxicity study. Secondly, kinetic analyses relate exposure to toxicology findings and contribute to the assessment of the relevance of these findings to clinical safety.

In toxicokinetic studies, the matrix of choice (e.g., blood, plasma, excreta, or tissues) should be sampled frequently enough to permit estimation of the exposure without interfering with normal conduct of the study or causing undue physiologic stress to the animals. The doses and duration chosen for toxicokinetic evaluations should be based on those used in the single- and multiple-dose toxicology studies.

O Investigational New Drug Application

- After the successful completion of preclinical research, Drug developer or sponsor, must submit an Investigational New Drug (IND) application to respective regulatory authority such as FDA in US, CDSCO in India etc in order to start clinical research.
- The IND filing is the formal process by which a sponsor requests approval for testing of a drug in human subjects.

In the IND application, following things are must included:

- Animal study data and toxicity data
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator
- Any additional data

After submitting IND, respective regulatory authority reviewed all the data and if satisfied, they grant the sponsor to begin clinical trial. It will take 30 -60 days after IND submission to get approval for clinical trial from the FDA.

The Investigator's Brochure: The Investigator's Brochure (IB) is an important document, not only required as a part of the IND but also prepared for presentation to potential clinical investigators and ultimately for presentation to the investigator's IRB(Institutional Review Board or Independent Review Board). The IB is a

compilation of the clinical and nonclinical data on the investigational product that is relevant to the study of the product in human subjects.

Its purpose is to provide the investigators and others involved in the trial with information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, and nonpromotional form that enables a clinician or potential investigator to understand it and make his or her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s), and the investigators are responsible for providing the up-to-date IB to the responsible IRBs.

The following provides the information that should be included in the IB –

1. Title Page - This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number and a reference to the number and date of the edition it supersedes be provided.

TITLE PAGE OF INVESTIGATOR'S BROCHURE (Example)

- Sponsor's Name: Product: Research Number: Name(s): Chemical, Generic (if approved)
- Trade Name(s) (if legally permissible and desired by the sponsor) Edition Number:
- Release Date:
- Replaces Previous Edition Number:
- Date:

2. Confidentiality Statement - The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

3. Contents of the Investigator's Brochure - The IB should contain the following sections, each with literature references where appropriate:

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies
 - 5.1. Nonclinical Pharmacology
 - 5.2. Pharmacokinetics and Product Metabolism in Animals
 - 5.3. Toxicology
6. Effects in Humans
 - 6.1. Pharmacokinetics and Product Metabolism in Humans
 - 6.2. Safety and Efficacy
 - 6.3. Marketing Experience
7. Summary of Data and Guidance for the Investigator
8. Publications
9. Reports (these references should be found at the end of each chapter.) and Appendices (if any)

O Clinical Phase of Drug Development: Pre-clinical research provides a basic idea about drug's safety in animal models, but it is not a substitute for human subjects. "Clinical research" refers to studies, or trials, that involve human subjects to establish the safety and efficacy of drug.

- **Clinical trials consist of 4 phases –**

*** Phase I –**

Study Participants: 20 to 100 healthy volunteers

Length of Study: Several months to one year

Purpose: Safety and Dose range

*** Phase II –**

Study Participants: 100 to 300 volunteers with the disease.

Length of Study: Up to 2 years

Purpose: Safety and Efficacy

*** Phase III-**

Study Participants: 300 to 3,000 volunteers who have the target disease

Length of Study: 1 to 4 years

Purpose: Confirm Efficacy and long term Safety, monitoring of adverse reactions

O New Drug Application (NDA)

- After the successful completion of clinical research, if the drug candidate proven satisfactory to be safe and effective for its intended use, then drug sponsor can submit New Drug Application (NDA) to respective regulatory authority in order to get marketing license and start commercial production.
- To submit New Drug Application (NDA) filing, drug sponsor must provide all the research data which are obtained from preclinical to Phase 3 clinical trial along with following documents –
- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information
- Location where the clinical trial studies have been conducted
- compliance Report of preclinical study
- Directions for use

NDA Review - After NDA received by the regulatory agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area that justify NDA filing.

At the conclusion of the review of NDA, there are 3 possible outcomes that can send to drug sponsor:

1. Not approvable- it display list of deficiencies and explain the cause of rejection.
2. Approvable – minor changes are suggested for the marketing approval
3. Approved for marketing.

It will take 6 – 12 months after NDA submission to get approval letter for marketing

* **Phase IV** –Phase IV trials are post-approval trials in which adverse drug reactions (ADRs) are monitored to ensure drug’s safety after being marketed. It is also called post-marketing surveillance studies. These studies carried out by drug sponsor, government agency or individual research organizations periodically after the drug being marketed.

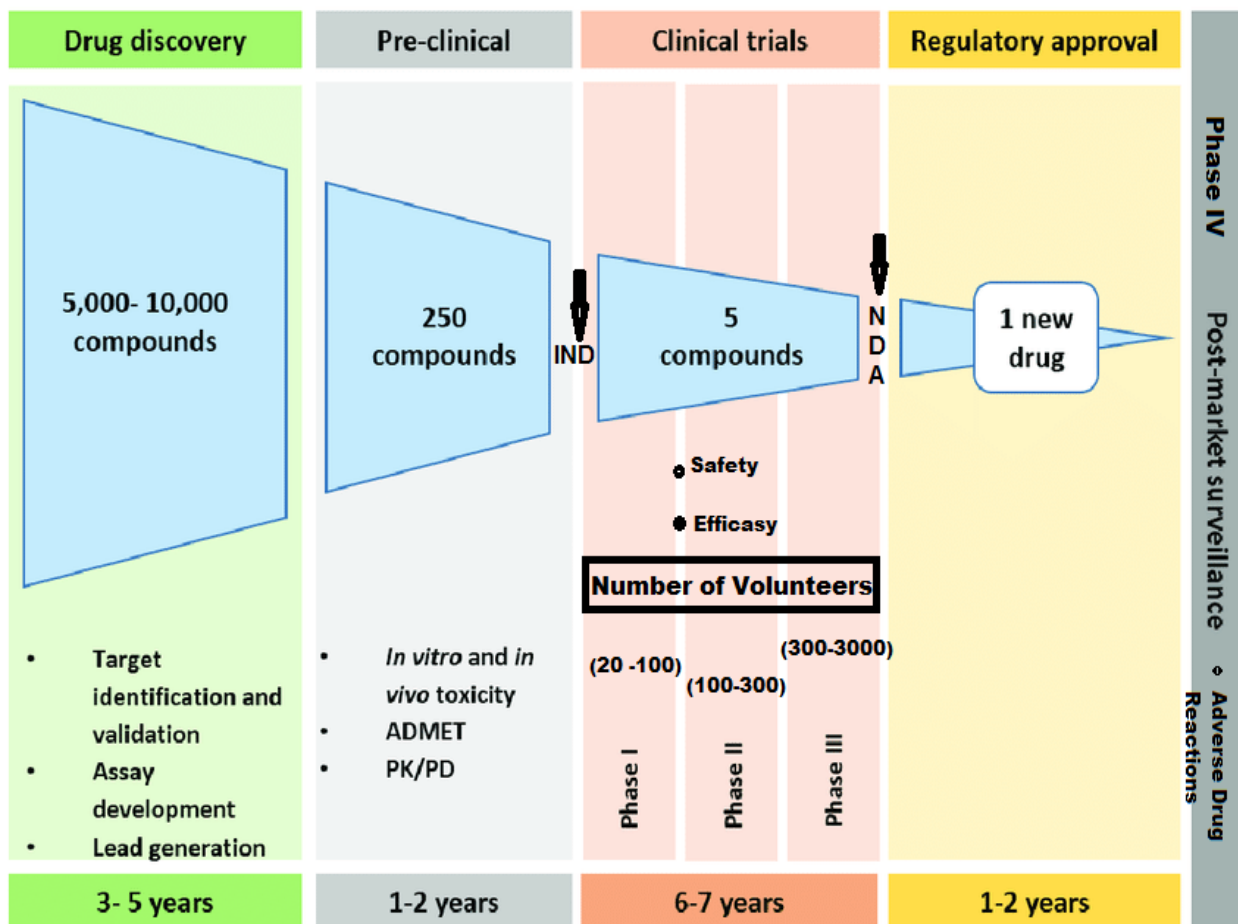


Figure 2 – Different Phases o drug development

O BE Study - Bioequivalence (BE) studies are performed to demonstrate that different formulations or regimens of drug product are similar to each other in terms of their therapeutic benefit (efficacy) and non therapeutic side effects (safety). They play a key and pivotal role in the drug development process by ensuring that when a patient switches to a new formulation in the marketplace, safety and efficacy will be maintained.

Bioequivalence studies are primarily used by pharmaceutical sponsors of new drug entities to demonstrate that the formulation used in Phase III confirmatory clinical trials is sufficiently similar to the final commercial formulation to be marketed following approval.

BE studies can be viewed as providing necessary and sufficient reassurance to regulators that the formulation to be marketed is the same as that used in the clinical confirmatory trials without the need to repeat the development program or to perform a therapeutic equivalence study in patients with clinical endpoints .

Bioequivalence studies must also be performed following substantial postmarketing formulation alteration. They are also used by what is termed the ‘generic’ pharmaceutical industry to gain market access for formulations of established drug therapies when the patent of the original sponsor’s formulation expires. When the original sponsors themselves perform a formulation change (for instance, change the site of manufacture) following approval, they often also must do a bioequivalence study to convince regulators that the new formula is safe and effective to market

Bioequivalence studies are usually conducted in male and female healthy volunteer subjects. Each individual subject is administered two formulations (T=Test or R=Reference) in one of two sequences of treatments (e.g., RT and TR), R is the ‘standard’ and T is the ‘new’ formulation.

Each administration is separated by a washout period appropriate to the drug under study; this washout period consists of five half-lives between administrations. Half-life is determined by looking at the elimination (after Cmax) part of the PK concentration versus time curve and is simply the length of time it takes the body to eliminate one-half of the amount of whatever drug is in the body at any given time. In general, if five half-lives go by, little to no drug should be left in the systemic circulation

Figure 3- Schematic Plan of a 2 × 2 Cross-over Study

Sequence Group	Period			Number of Subjects
	1	Washout	2	
1 (RT)	R	—	T	<i>n</i> /2
2 (TR)	T	—	R	<i>n</i> /2
R=Reference, T=Test				

Such a design is termed a 2 × 2 cross-over [237] and is a type of design typically applied in bioequivalence trials.

To demonstrate equivalence in plasma concentration profiles, rate and extent of bioavailability of the drug substance in plasma must be sufficiently similar so as to meet the regulatory standard for showing that exposure of the body to the drug substance is the same between formulations. For this purpose, Cmax (rate)

and AUC (extent) are typically used as summary measures for the plasma concentration curves and are required to be demonstrated as equivalent under preset decision rules to achieve regulatory approval.

O Clinical Trial Protocol: The clinical trial protocol is a document that describes how a clinical trial will be conducted (the objective(s), design, methodology, statistical considerations and organization of a clinical trial,) and ensures the safety of the trial subjects and integrity of the data collected. Clinical trials carried out in accordance with the guidelines of Good Clinical Practice (GCP) and ICH. The GCP-ICH regulations are found in - **E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1)**.

The contents of a trial protocol should generally include the following topics–

1. General Information

1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

1.2 Name and address of the sponsor and monitor (if other than the sponsor).

1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert for the trial.

1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

2. Background Information

2.1 Name and description of the investigational product(s).

2.2 A summary of findings from nonclinical studies that potentially have clinical significance and are relevant to the trial.

2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

2.6 Description of the population to be studied.

2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

3. Trial Objectives and Purpose - A detailed description of the objectives and the purpose of the trial.

4. Trial Design -The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.

A description of the trial design should include:

4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

4.3 A description of the measures taken to minimize/avoid bias, including:

(a) Randomization.

(b) Blinding.

4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

5. Selection and Withdrawal of Subjects -

5.1 Subject inclusion criteria.

5.2 Subject exclusion criteria.

5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6. Treatment of Subjects -

6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.3 Procedures for monitoring subject compliance.

7. Assessment of Efficacy -

7.1 Specification of the efficacy parameters.

7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

8. Assessment of Safety -

8.1 Specification of safety parameters.

8.2 The methods and timing for assessing, recording, and analysing safety parameters.

8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

8.4 The type and duration of the follow-up of subjects after adverse events.

9. Statistics -

9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis.

9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for the choice of sample size including clinical justification.

9.3 The level of significance to be used.

9.4 Criteria for the termination of the trial.

9.5 Procedure for accounting for missing, unused, and spurious data.

9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

10. Direct Access to Source Data/Documents -

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

11. Quality Control and Quality Assurance

12. Ethics - Description of ethical considerations relating to the trial.

13. Data Handling and Record Keeping

14. Financing and Insurance- Financing and insurance if not addressed in a separate agreement.

15. Publication Policy- Publication policy, if not addressed in a separate agreement.

16. Supplements

O Biostatistics in Pharmaceutical Product Development -

Statistics plays an important role in drug product development. Its use is necessary for planning and analyzing trials and using statistics correctly is crucial for the success of drug development programs. Applications of biostatistics in pharmaceutical product development are as follows –

- Provide scientific method thinking into the target identification process
- Assess the ability to Quantify effect on target of interest
 - Does animal model translate into human?
 - How will effective dose be identified?
- Provide critical input into quantification of risk (Risk assessment)
- Agree criteria for stopping dose escalation
- Assist in establishing go/no go decision criteria (significance testing-p value)
- Review of safety margins from animal data
- Assist in appropriate study design selection and of Primary endpoints for studies.
- Design and implementation of randomization systems in study design.
- Helps in sample collection, data analysis and refinement, error and bias detection.
- Design and optimize formulation, optimize process parameters in pilot plant scale up.
- Used as Analytical methods validation tool.

Key Statistical supports in different phases of drug development are summarize below –

Table 4 - Drug Product Development and Statistical Support

Milestones	Activities	Statistical support
Nominate an API for clinical development	Discover the API and perform various preclinical studies	Multiple comparison techniques for combinatorial chemists; analysis of genomic data; design and analysis of animal safety studies, etc.
Perform Phase I clinical studies	Determine Phase I dosage type (e.g., liquid, capsule, tablet [or new technology])	Analysis of historical data; statistical thinking (design and analyze experiments)
	Excipient compatibility studies	Design and analyze experiments
	Accelerated stability studies	Regression analysis
Perform Phase IIA (dose ranging) and IIB (proof of concept) clinical studies	Determine Phase II dosage type (new technology)	Analysis of historical data; statistical thinking (design and analyze experiments)
	Evaluate excipient compatibility (if not performed previously)	Design and analyze experiments
	Develop Phase II dosage formulation	Design and analyze factorial and/or mixture experiments
	Develop Phase II manufacturing process	Design and analyze factorial and/or response surface experiments
Perform Phase III clinical studies	(If necessary, determine Phase III dosage type)	(Design and analyze experiments to investigate scalability and/or economic concerns with Phase II dosage type)
	Develop and/or scale Phase III dosage formulation	Design and analyze factorial and/or mixture experiments
	Develop and/or scale Phase III manufacturing process	Design and analyze factorial, mechanistic, and/or response surface experiments
	Develop PAT applications	Multivariate analysis
	Transfer technology to commercial manufacturing division	Write reports and consult
Submit new-drug application	Develop and/or scale commercial formulation and process	Design and analyze factorial, mechanistic, mixture, and/or response surface experiments
	Define design and knowledge spaces for DP formulation and process	Design and analyze product- and process-understanding experiments
	Conduct ICH campaign	Analyze ICH stability studies (set expiry)
Milestones	Activities	Statistical support
Produce commercial product	Establish QA procedures	Assess process capability and establish quality systems to control the process (SPC, PAT, establish sampling plans, etc.)
	Monitor DP stability	Analyze data from annual stability lots
	Improve the process	Data mining, DoE, Six Sigma techniques, Lean techniques, JIT manufacturing, etc.

O Data Presentation for FDA Submissions: Following points to be consider for NDA submissions or other regulatory submissions –

1. TEXT EXPOSITION –

A. Content - Most NDA submissions contain an enormous amount of data, which cannot be presented entirely within the body of a document. Although all the data collected for an individual subject or patient (or groups of subjects or patients) may be important, critical judgment must be exercised in the selection of key data for presentation and discussion within a given document. Data necessary for the development of a specific thesis should be presented within the body of the document rather than placed into a remote appendix, which will impede the review.

Less important data can be summarized briefly, clearly referenced in text, and placed in appendices. Any data submitted will have to be evaluated, so the inclusion of extraneous data will slow the review of the application. The submission should note the existence of such data and have it available upon request of the FDA.

B. Tone - The tone of the text should be formal without being stilted. Avoid legal language on the one hand and colloquial or informal language on the other.

C. Conciseness - The following points address ways of making NDA documents more concise.

1. Keep the language simple and straightforward.

2. Use acronyms and initialisms to speed up the flow of text if they are easily recognized and have been spelled out at first mention. Those that may be confused with another used in the same document should be spelled out.

3. Eliminate redundancies. A careful review of the text will find many words, phrases, and even sentences that can be omitted. Sentences can often be combined by the deletion of redundant phrases, thus improving the flow of the text.

D. Correctness - The textual presentation should agree with the tabular data in the document; in turn, the tabular data should agree with the data source (which agrees with the case report for and other clinical documentation). This is critical to the scientific merit of the submission. When lack of agreement between in-text data and source documents is found, the entire submission may be suspect, and the reviewer will be inclined to spend much more time evaluating the raw data to be sure of the conclusions.

E. Consistency - Consistent punctuation, capitalization, abbreviations, and other styling conventions are much desired in all documents with proper judgment.

F. Clarity -The FDA reviewer should be able to read through an application expeditiously and not have to stop to try to discern the meaning of a textual presentation. Clarity is facilitated by careful attention to the following:

1. Punctuation.

2. Sentence structure and length.

3. Misplaced modifiers.

4. Parallelism. Because much of the data in an NDA involves comparisons of one group to another, parallel structure is important in presenting the data.

G. Outline of Sections and Subsections - The clear relationship of one section to another is critical to the review of a document.

The decimal system is a very popular outlining system; it is easy to use and can be set up automatically in most current word processing software applications. Another popular outlining system is the alphanumeric system, where letters and numbers alternate as section headers.

H. Indenting - Avoid indenting large sections of text. Most text should be flush to the left margin with appropriate headers to identify the section. Multiple and sequential indenting wastes **of** space and is confusing. Short lists are appropriately indented, and conventions like indenting with bullets are useful to break up long sections of text.

I. Global to Specific -

For any section, begin with global statements or data and then discuss the specifics. For example, in the discussion of adverse events, the overall presentation of the events should precede the presentation by severity, by relationship, by subgroup, etc. It is particularly important in the discussion of the populations evaluated in a particular document. Begin with the all inclusive population first, then define the subpopulations.

2. TABULAR PRESENTATION -

In-text, tables should be used whenever they simplify the presentation and allow for substantial reduction in text. Comprehensive multipage tables that interrupt text should be avoided, if possible, unless they are critical. However, if the tables are very important, they can be placed in the same volume in an appendix. Usually, data can be collapsed to be included in the in-text table, with reference to the full table in an easy-to-locate appendix. It should be mentioned that any tables, figures, or graphs in the appendices must have in-text references. Information from the tables should not be repeated in the text except as part of a concluding statement about the tabular data or trends seen in the data. The commentary on data from the tables should precede the table, beginning with an introduction to the table by number and a statement identifying what type of data it contains.

Additional commentary related to the table but not derived from the tabular data may follow the table.

A. Title - All tables require concise but descriptive titles.

B. Data Source - Every table should identify the source of the data contained in it. This is usually done in a footnote to the table. The volume and page numbers will be inserted at the end of the project.

C. Footnotes - Footnotes should be assigned letters (superscripted), not symbols or numbers, which can be confused with the data. In multipage tables, footnotes should be assigned letters in the order in which they appear on the specific page of the table. Always begin such tables on a new page to avoid changing the footnotes as the tables shift with the addition of preceding text.

D. Orientation - Portrait tables are always preferable to landscape tables. If data appear not to fit in the portrait orientation, try changing the axes of the table, so that the axis with more individual descriptors is vertical, whereas the axis with fewer items is horizontal (column headings). Also consider revising the table into separate sections under the same column headers, with descriptive headings for each section spanning the width of the table.

E. Order of Data Presentation - In multiple tables with similar data, present the data in the same order as much as possible. If the first column always has the active drug and the second column the placebo or comparative agent, then keep this order throughout the tables. In the analysis of data by demographic or disease subgroup, it is helpful to keep the subgroup of concern

(i.e., women, the elderly, racial subgroups, impaired renal function) in the same column in each table.

F. Present Meaningful Data Together - Try to present the data that will be evaluated and compared as close together as possible rather than scattered around the table.

O Management of Clinical Trials – The key elements in managing clinical programs are as follows -.

* **Investigator selection** - US GCP Federal Regulations and ICH GCP Guidelines mandate that a sponsor select only investigators qualified by training and experience as appropriate experts to evaluate an investigational product (21 CFR 312.53). A similar reference appears in the ICH GCP Guidelines as well.

* **Preinvestigational site visits (PISV)** - After prescreening of potential investigators is established, it is vitally important that a PISV be conducted at the investigational site with the investigator and their staff to continue to assess their ability to conduct the trial. The PISV is usually performed by the monitor or an authorized individual appointed by the sponsor company.

***Study initiation visits (SIV)** – Once the PISV is complete, an SIV is the next step. The initiation visit is a training programme. This is the last training on the protocol that the investigators and their staffs will have before beginning to recruit and enroll subjects into the trial. During this meeting, the monitor will review the following in details – Study Protocol, Adverse experience and serious adverse experience reporting documentation, reports, Product dispensation and accountability, Case Report Form (CRF) completion, Review of regulatory documents and Source documentation.

***Trial conduct and execution** - There are several other key components to trial execution that will require special attention: subject recruitment, the informed consent, IRBs/IEC review product accountability, adverse experience and adverse reaction reporting, financial disclosure, and record retention. Each is critical in the overall success of a clinical trial.

* **Periodic monitoring visits** - Both the CFR and the ICH GCP guidelines require that the sponsor monitor the progress of the clinical trial at the site where the trial is being conducted. The overall purpose of these periodic monitoring visits by the sponsor's monitor is to assure that the investigators and their staffs follow GCP regulations and guidelines and adhere to the protocol to assure that the rights of the subjects participating in the clinical trial are being protected and that the data reported is complete, accurate, and verifiable.

* **Subject Recruitment**- One of the surest ways to decrease the overall time to complete a clinical trial is to recruit subjects into the trial in the shortest amount of time. The secret to effective subject recruitment is planning on how and where to recruit a subject population. In planning for recruitment, one must know and understand the subject population that will meet the protocol criteria. What motivates these subjects to participate in the clinical trial? What kind of medical treatment are they presently receiving, and who are they seeing to get this treatment? What is the present status of their medical condition?

***Product accountability** - Clinical trials evaluate new investigational drug/devices which have not yet received marketing authorization from the appropriate health care authority. Therefore it is mandatory that strict control be maintained on any investigational product. The investigator is responsible for the accountability of the test product. Investigational products should only be prescribed by the investigator or authorized sub investigators. The sponsor is responsible for retrieving/verifying the disposition of all used and unused product. Detailed records of product accountability must be maintained throughout a trial with information on the date dispensed, the quantity dispensed, the subject identifier (subject number), and the batch number of product prescribed.

***AE and ADR reporting** -Drug safety and adverse reactions are closely related in an inversely proportional manner. In the United States, drug safety is under strict legislative control mandated by the FDA. Federal regulations require a sponsor to report adverse experiences and reactions for an investigational product at both the investigational and the post marketing stages.

***Financial disclosure** - One of the newest components of a clinical trial is financial disclosure. This regulation initiated in the United States on February 2, 1999, is required on all current or ongoing clinical trials filed in an IND. Financial disclosure is defined by the FDA as compensation related to the outcome of the study, proprietary interest in the product (e.g., patent), significant equity interest in the sponsor of the study, significant payments of other sorts to the investigator or institution (e.g., equipment, honorariums). The reason for this regulation is to assure the FDA that appropriate steps were taken to minimize bias in the design, conduct, reporting, and analysis of the studies even when the investigator has a financial interest in a new product.

***Study close-out visits (SCV)** - Once a trial is completed at an investigational site, the study must be appropriately closed. This cannot occur until all of the subjects have completed the course of the trial, or were dropped or withdrawn, and all data queries and issues have been addressed and resolved in the final evaluations. Only when this is done can the monitor proceed to a close-out visit. The following checklist will guide the monitor in completing the SCV:

All subjects entered in the trial have been accounted for.

All CRF pages have been completed and retrieved.

All data queries have been resolved.

All AEs and ADRs have been reported and followed up.

All investigational product has been accounted for and disposed of or returned to the sponsor.

All remaining supplies (CRFs, ancillary supplies) are returned or disposed of properly.

Regulatory records are complete and organized in the Trial Binder.

All outstanding issues are addressed.

*** Records retention and inspections** - Record retention is critical to the ongoing viability of the study data. The FDA or other health care authorities may conduct an on-site inspection to verify the data from a given site at some time after submission of the New Drug Application (NDA). This information must be readily available at the site. Both the CFR and the ICH require that the records be retained for two years after the date of a marketing application is approved.

List of Abbreviations:

ADME - Absorption, distribution, metabolism, excretion

ADR – Adverse Drug Reaction

AUC - Area under the curve

ANDA- Abbreviated New Drug Application (for a generic drug)

DoE – Design of Experiment

CFR - *Code of Federal Regulations* (usually cited by part and chapter, as 21 CFR 211)

EU- European Union

GCP- Good Clinical Practice

GLP - Good Laboratory Practice

IB - Investigator's Brochure

ICH - International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC- Independent Ethics Committee

IND - Investigational New Drug Application

IRB - Institutional Review Board, sometimes Independent Review Board.

IRC - Institutes Review Committee

IRD - International Registration Document

ISO -International Organisation for Standardisation

MAA -Marketing Authorization Application

MTD -Maximum tolerated dose

NCE - New chemical entity

NDA- New Drug Application

PAT- Process Analytical Technology

SPC – Statistical Process Control

USFDA - U.S. Federal Drug Administration

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