BP702 T.INDUSTRIALPHARMACYII

IndustrialPharmacy(II)–UnitIII

Regulatory affairs - Regulatory Affairs (RA), also called Government Affairs, is a profession developedfrom 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 iscomposedofa group of people whoactasa liaisonbetweenthegovernment, 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.

RegulationofDrugproductsinvolvefollowingareas –

- Non-clinicalandClinicalDrugDevelopmentGuidelines Licensing
- (Patent)
- DrugRegistration
- Manufacturing
- QualityandsafetyGuidance
- Pricing and Trademark
- Marketing, Import and Distribution of Drug products
- Pharmacovigilance(AdverseDrugReactionsmonitoring)

Table1-HistoricalOverviewofRA(Keyregulatoryeventswithyear)

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

RegulatoryAuthorities-

Public health being the prime concern, it is necessary that the drug/drug product available for human/veterinary useand medical devices must not only be effectivebut also besafefor theintended 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.

RoleofDrugRegulatoryAffairsDepartment:

A) InDevelopmentphase-

- Ensuringthatthelegislativerequirementsaremet-

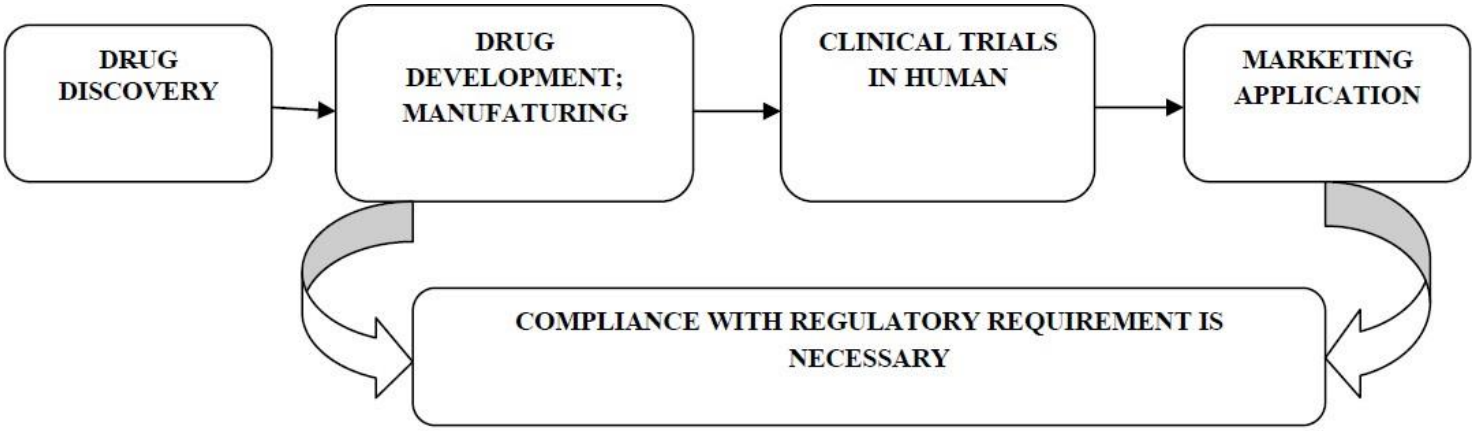

FIGURE 1: Regulation of drug approval process

RecruitScientificAdvice-authorities

–Adviceondevelopmentstudiestodemonstratesafety,qualityandefficacyparameters.

- Setupregulatorystrategy.
- Participateincross-functionalprojectteams.
- Ensureapplicationofguidelinesforclinicaltrials.
- Submissionofapplicationtoconductclinicaltrials.
- Managingtheregulatorysubmission-

  –Minimizetimetomarket(everydaycounts!)

  –Adviceonaglobaldevelopmentplan
- Optimizesubmissionstrategies-
  - Dossierpreparation
  - Format,documentre-uses
  - Electronicsubmissions
  - Reviewhigh-leveldocuments/reports
- Interactwithcommercialsideofbusinesssuchaspricingandreimbursement.

B) Inapprovalphase-

- Checkprogressofevaluationandanticipatequestions.
- Clarifyraisedquestions,planresponseandstrategieswithotherdepartments.
- Planandmanageagencymeetings/hearings.
- NegotiateapprovalandProductInformationwithagencies.

C) Inpostapprovalphase-

- Compliance
- Submissionofvariations/amendments
- Renewals
- Pharmacovigilance

- Productinformationreview
- Newindications/newformulations
- Regulatoryinputtodevelopmentplans/RegulatoryIntelligence.

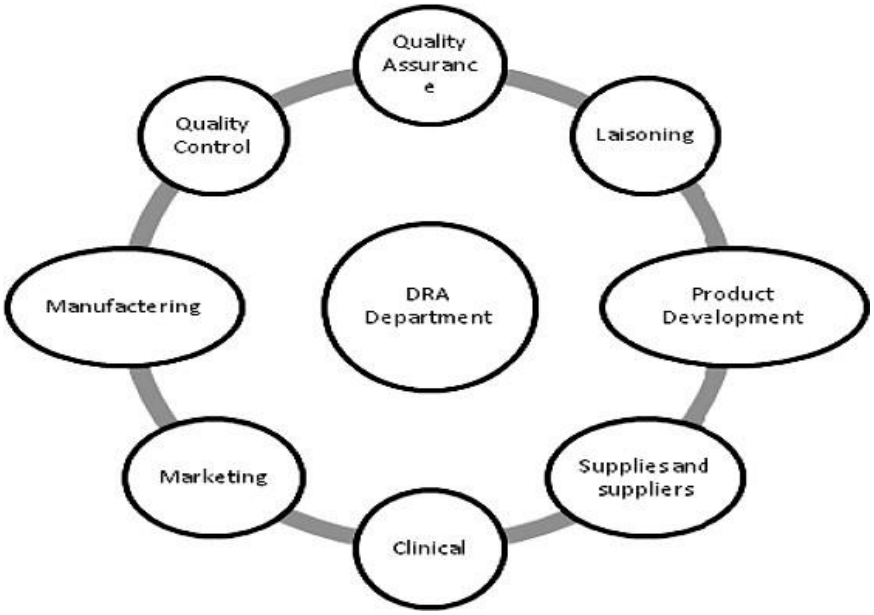

Figure2–VariousRoleofDrugRegulatoryAffairsDepartment Responsibility

of the Regulatory Affairs Professionals -

ØEnsuringthattheir companiescomplywithallofthe regulationsandlawspertainingtotheirbusiness.

ØWorkingwithfederal, stateandlocalregulatoryagenciesandpersonnel onspecificissuesrelatedtotheir business.

ØAdvisingcompaniesontheregulatoryaspectsandclimatethatwouldaffecttheirproposed activities.

ØKeepintouchwithinternationallegislation,guidelinesandcustomerpractices. Ø
Keep up to the date with a company's product range.
ØCollect, collate, andevaluatethescientificdata thattheir researchanddevelopmentcolleaguesare generating.
ØFormulateregulatorystrategies for allappropriateregulatorysubmissions suchasdomestic, international and/or contract projects.
ØCoordinate, prepareandreviewallappropriatedocumentsfor exampledossier andsubmit themto regulatory authorities within a specified time frame in conjugation with the organization.
ØPrepareandreviewofSOPsrelatedtoRA. ReviewofBMR,MFR,changecontrol andother relevant documents.
ØMonitor theprogressofallregistrationsubmission.
ØMaintainapprovedapplicationsandtherecordofregistrationfeespaidagainstsubmissionofDMF'sand

other documents.

ØRespondtoqueriesandensurethatregistration/approvalaregrantedwithout delay.

ØParticipateinR&Dtraining, Pilotplant ScaleUp,andPostMarketingSurveillance(ADR).

ØManageandreviewauditreportsandcompliance, regulatoryandcustomerinspections.

ØProvideaccurateandcompleteinformationabout thequality, safetyandeffectiveness oftheproduct tothe physicians and other healthcare professionals.

Regulatoryrequirementsfordrug approval:

DrugDevelopmentTeams-Mostpharmaceuticalandbiotechnologyfirms employdrugdevelopmentproject 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 approachestothedevelopment process. Allteammembersmust workcloselytogether toensurethat adrugis both safe and efficacious.

Theresponsibilitiesoftheseprojectteamsinclude-

1. Reviewingresearchresultsfromexperimentsconductedbyanyofthevariousscientificdisciplines.

2. Integratingnewresearchresultswithpreviouslygenerateddata.

3. Planningresearchstudiestofurther characterizea drugcandidate.

4. Preparingadetaileddrugdevelopmentplan,includingdesignationofkeypointsordevelopment milestones, generating a timeline for completion, and defining the critical path.

5. Monitoring thestatus of research studies to ensurethat they arebeing conducted according to thetimeline andcriticalpathinthedevelopment planand, ifappropriate, modifyingtheplanasnewinformationbecomes available.

6. Comparingresearchresultsanddevelopmentstatusandtimelines withdrugcandidatesunderdevelopment by competitors.

7. Conductingappropriatemarketsurveystoensurethatthedevelopment ofa drugcandidateis economically justified and continues to meet a medical need.

8. Reportingthestatusofthedrugdevelopment programtomanagement andmakingrecommendationsonthe continued development of the drug candidate.

Drugdevelopmentteamsconsistoffollowinggroupofteams-

1. Discovery/developmentTeam

The discovery and development groups are comprised of the basic scientists and chemists who created the newmolecule.This groupsynthesizesdrugsubstancesfor“drug-screening,”pharmacology,andtoxicology studies, and also prepares clinical supplies.

2. Nonclinicalpharmacologyandtoxicology Team

This group studies the drug product in animal models for efficacy and safety in order to identify potential efficacyandsafetyissuesinhumans. It iscriticalfor theclinicalanddevelopment groupstoworkcloselywith the lexicologists in the design of animal studies to ensure their relevance to the clinical environment.

3. ClinicalresearchTeam

Clinicalresearch has theultimateresponsibilityfor testingdrugproducts in humans:themonitoringof drug safety rests squarely on the shoulders of clinical research. Clinical trials must be science-based with proper statisticalmethodologiesandhaveclinicallyrelevant endpoints. Clinicalresearchinteractsdirectlywiththe FDA and is responsible for the generation of study reports with input from biostatisticians and regulatory affairs. Clinicalresearchcanalso generatethepublicationsnecessaryfor themarketingofanydrugproduct.

4. RegulatoryaffairsTeam

Theregulatoryaffairsdepartmentistheinterfacewiththe FDA. Itistheir responsibilitytoensurecompliance with the rules and regulations established by the Federal Food Drug and Cosmetic Act and its amendments.

5. MarketingTeam

The marketing group has theultimateresponsibilityfor marketingandsellingthedrug. As a result, they need product, labelingthat differentiatestheir drugfromthosealreadymarketed. Marketinghastoprovidecreative concepts for the prescribing physician, the patient, and the company's senior management. They also have to make sure that, budget goals arc 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. LegalTeam

In order for a drug to befinancially successful, patent protection is a key element. Thelegal group must submit patents at theappropriatetimeanddoallinits power toavoidlawsuits frompotentialcompetitors.The legal group also ensures that neither the FDA nor the other organization or company will challengeadvertising and promotional materials.

7. ManagementTeam–Theyco-ordinatewithalltherespectiveteamsandresponsiblefor successful completion of project in a time bound manner.

PharmaceuticalDrugDevelopment:

- PharmaceuticalDrugDevelopment is aprocess ofbringinga newlysynthesized drugmoleculetothemarket once a lead compound has been identified through the process of drug discovery.

- These newly synthesized drug molecules which also known asNew 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,theprocessofdrugdevelopmentcanbedividedintopre-clinical/nonclinicalandclinicalphases.

- **Pre-clinical or Non- clinical Phase of Drug Development:** Pre-clinical Drug Development involves pharmacologicalandtoxicologicalassessment of thepotentialnew druginanimal models inorder toestablish its safety and efficacy before the administration to human volunteers in clinical trial phase.

- Pharmacologicalandtoxicologicalassessment ofthepotential drugcandidateis carried out byboth 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.
- Suchpreclinicalstudiescanbetakeup to2yearstocomplete.

OPre-clinicalDrugDevelopmentinvolvesfollowingmajortypeofstudies–

1. Pharmacologicalstudies-

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

Themaintaskofpharmacokineticstudies is tofindan optimal doselevelandtoprovideinformationabout 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.

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

Table2-Recommendednon-clinicalassaysofADME/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 beconducted 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 todetermine 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 studiesare 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 specificactivityhighenoughtobemeasurableafterdosing.Also,thelabelneedstobeinapositionwhereit

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. Studyof metaboliteprofileinurineandbile carried out to determinetheamount 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) PharmacodynamicprofleStudy–Pharmacodynamicstudiesdealmorespecificallywithfollowings-

a) Primarypharmacodynamic(PD)study-StudyPhysiologicaleffectsofdrug

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 potentialpharmacological effects inconcentrationranges oftherespectivesubstanceon whichaneffect 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 corebatteryareinvestigated. This is notablydonewith other major organsystems suchas thegastrointestinal, renal or the immune system.

2. ToxicologicalStudies-Toxicologydefinesthepreclinicalpartofthesafetyassessmentduringdrug development. By conducting toxicity studies, possible hazards and risks are identified.

i) Acutetoxicity(Singledose) andChronictoxicity(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 isadministered by atleasttwo 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 bea non-rodent. For **Repeated-dose**toxicitystudysmall doses ofdrugadministered7daysa 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 potentialteratogenicity 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**.

SegmentI,evaluatesfertilityandgeneralreproductiveperformanceinrats.

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, neonatalviability, 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 premating dosing of at least 4 weeks and with dosing continuingthroughoutthematingperiod.Histopathologyofthesetestsandspermanalysisisusedto

detect effects on spermatogenesis. Female fertility is determined by premating 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 embryotoicity or teratogenic effects and are conducted in a rodent and nonrodent species. The drug candidateis administered during theperiod 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 beforeanticipatedparturition. For rats, half of the fetuses are examinedfor visceral alterations andthe other half areevaluatedfor skeletalabnormalities. For rabbits, microdissectiontechniques 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 damsfromimplantationtotheendof lactation. At thetimeof weaning, normallyonemaleandonefemale 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 vitroandinvivomethods. Thestandardbatteryof testsrecommendedbyICH 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

Table3-StandardGeneticToxicologyTestBattery(ICH)

iv) Carcinogenicity Study –Long-termcarcinogenicitystudy is carried out, particularlyifthedrug is usedfor administration over prolonged period (≥ 6 months). In such type of study animal is observed for the development of tumors.

Carcinogenicity studies areconducted in two rodent species (mostly ratsand mice) over a long-termperiod of 2 years. Two types of dose is used for the study – 1. Maximum tolerated dose (MTD) and 2. 25-fold AUCratio (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.Immunotoxicitywhich maybeinvestigatedduringrepeateddosetoxicitystudies.Itidentifiesadverse

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 weighedor 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. Secondarily, 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 permitestimation of the exposure withoutinterfering 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.

OInvestigationalNewDrug Application

- After thesuccessfulcompletionofpreclinicalresearch,Drugdeveloper or sponsor,mustsubmitan InvestigationalNewDrug(IND) applicationto respectiveregulatoryauthoritysuchas FDAin US, CDSCO in India etc in order to start clinical research.
- TheINDfilingistheformalprocess bywhicha sponsorrequestsapprovalfor testingofa drugin human subjects.

IntheINDapplication, followingthingsaremustincluded:

- Animalstudydataandtoxicitydata
- Manufacturinginformation
- Clinicalprotocols(studyplans)forstudiestobeconducted
- Datafromanypriorhumanresearch
- Informationabouttheinvestigator
- Anyadditionaldata

After submitting IND, respective regulatory authority reviewed all the data and if satisfied, they grant the sponsor tobeginclinicaltrial. It willtake30 -60daysafter INDsubmissiontoget approvalfor clinicaltrial 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 presentationtotheinvestigator'sIRB(InstitutionalReviewBoardorIndependentReviewBoard).TheIBisa

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.

TheIB also provides insight to support theclinical management of thestudy subjects during thecourse of the clinical trial. The information should be presented in a concise, simple, objective, and nonpromotional form that enablesa clinicianor potentialinvestigator tounderstandit andmakehisor her ownunbiasedrisk-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.

TheIBshouldbereviewedat least annuallyandrevisedas necessaryincompliancewitha sponsor's written procedures.
Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s), andtheinvestigators areresponsiblefor providingtheupto- dateIBtotheresponsibleIRBs.

Thefollowingprovides theinformationthat shouldbeincludedintheIB–

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 desiredbythesponsor), andthereleasedate. It is alsosuggestedthat aneditionnumber andareferencetothe number and date of the edition it supersedes be provided.

TITLEPAGEOFINVESTIGATOR'SBROCHURE(Example)
- Sponsor'sName:Product:ResearchNumber:Name(s):Chemical,Generic(ifapproved)
- TradeName(s)(iflegallypermissibleanddesiredbythesponsor)EditionNumber:
- ReleaseDate:
- ReplacesPreviousEditionNumber:
- Date:

2. Confidentiality Statement - The sponsor may wish to include a statement instructing the investigator/ recipients totreat theIBasa confidentialdocument for thesoleinformationanduseofthe investigator's team and the IRB/IEC.

3. ContentsoftheInvestigator'sBrochure -TheIBshouldcontainthefollowingsections, eachwith literature references where appropriate:

1. TableofContents
2. Summary
3. Introduction
4. Physical,Chemical,andPharmaceuticalPropertiesandFormulation
5. NonclinicalStudies
   NonclinicalPharmacology
   PharmacokineticsandProductMetabolisminAnimals
   Toxicology
6. EffectsinHumans
   PharmacokineticsandProductMetabolisminHumans
   SafetyandEfficacy
   MarketingExperience
7. SummaryofDataandGuidancefortheInvestigator
8. Publications
9. Reports(thesereferencesshouldbefoundattheendofeachchapter.)andAppendices(ifany)

O Clinical Phase of Drug Development: Pre-clinical research provides a basic idea about drug's safety in animalmodels, butitisnota substitutefor humansubjects."Clinicalresearch"referstostudies, or trials,that involve human subjects to establish the safety and efficacy of drug.

- **Clinicaltrialsconsistof4phases–**

*** PhaseI–**

StudyParticipants:20to100healthyvolunteers **Length of Study:** Several months to one year **Purpose:**Safety and Dose range

*** PhaseII–**

StudyParticipants:100to300volunteerswiththedisease.

LengthofStudy: Up to2years

Purpose: SafetyandEfficacy

*** PhaseIII-**

Study Participants:300to3,000volunteerswhohavethetarget disease

LengthofStudy: 1to4years

Purpose: ConfirmEfficacyandlongtermSafety,monitoring ofadversereactions

ONewDrugApplication(NDA)

- After the successful completion of clinical research, if the drug candidate proven satisfactory to be safeandeffectivefor itsintendeduse, thendrugsponsor cansubmit NewDrugApplication(NDA)to respective regulatory authority in order to get marketing license and start commercial production.
- Tosubmit NewDrugApplication(NDA)filing, drugsponsor must provideallthe researchdata which are obtained frompreclinical to Phase 3 clinical trial along with followingdocuments –
- Proposedlabeling
- Safetyupdates
- Drugabuse information
- Patentinformation
- Locationwheretheclinicaltrialstudieshavebeenconducted
- complianceReportofpreclinicalstudy
- Directionsforuse

NDA Review - After NDA received by the regulatory agency, it undergoes a technical screening. This evaluationensuresthatsufficient dataandinformationhavebeensubmittedineacharea thatjustifyNDA filing.

At theconclusionofthereviewofNDA,thereare3 possibleoutcomesthatcansendto drugsponsor:

1. Notapprovable-itdisplaylistofdeficienciesandexplainthecauseofrejection.
2. Approvable–minorchangesaresuggestedforthemarketingapproval
3. Approvedformarketing.

Itwilltake6 –12monthsafterNDAsubmissiontogetapprovalletterformarketing

*** 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 studiescarriedoutbydrugsponsor,governmentagencyor individualresearchorganizationsperiodicallyafter the drug being marketed.

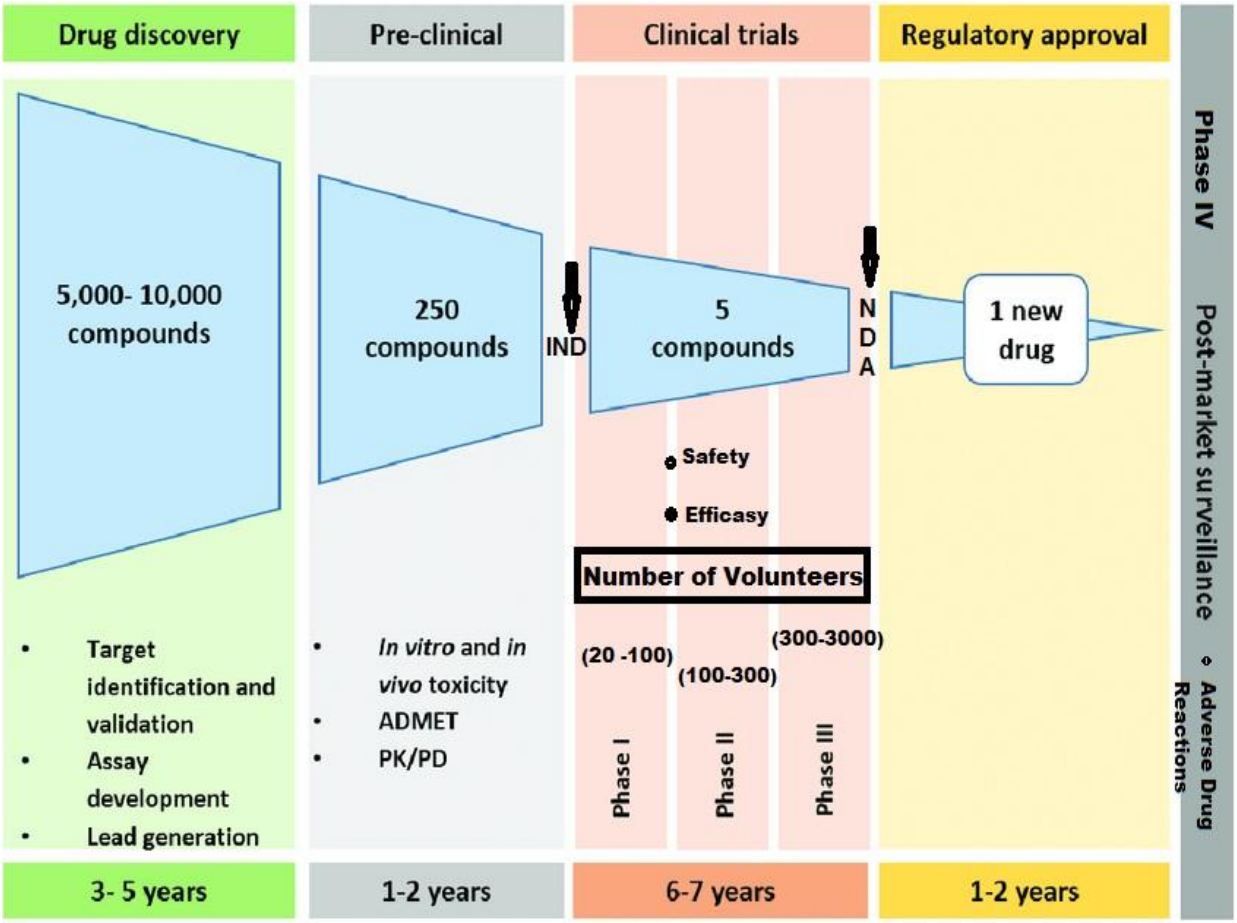

Figure2–DifferentPhasesodrugdevelopment

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 therapeuticsideeffects (safety). Theyplaya keyandpivotalroleinthedrug development process by ensuring that when a patient switches to a new formulation in the marketplace, safety and efficacy will be maintained.

Bioequivalencestudies areprimarilyusedbypharmaceuticalsponsors ofnewdrug entities to demonstratethat 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.

Eachadministrationis separatedbya washout periodappropriatetothedrugunder 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

Figure3-SchematicPlanofa2×2Cross-overStudy

Sequence Group	Period			Number of Subjects
	1	Washout	2	
1(RT)	R	—	T	$n/2$
2(TR)	T	—	R	$n/2$
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 exposureofthe body to thedrug substanceisthe same betweenformulations.Forthispurpose,Cmax(rate)

andAUC(extent)aretypicallyusedassummarymeasuresfortheplasmaconcentrationcurvesandare 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 aclinical trial,)andensuresthesafetyofthetrialsubjectsandintegrityofthedata collected. Clinicaltrialscarriedout in accordance with the guidelinesof Good Clinical Practice (GCP) and ICH. The GCP-ICH regulations arefound in - **E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6 (R1).**

Thecontentsofatrialprotocolshouldgenerallyincludethefollowingtopics–

1. GeneralInformation

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

Nameandaddressofthesponsor andmonitor (ifother thanthesponsor).

Nameandtitleoftheperson(s)authorizedtosigntheprotocolandtheprotocolamendment(s)forthe sponsor.

Name,title,address,andtelephonenumber(s)ofthesponsor's medicalexpertforthetrial.

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).

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).

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. BackgroundInformation

Nameanddescriptionoftheinvestigationalproduct(s).

Asummaryof findings fromnonclinical studies that potentiallyhaveclinical significanceandarerelevant to the trial.

Summaryoftheknownandpotentialrisksandbenefits,ifany, tohumansubjects.

Descriptionofandjustificationforthe route ofadministration,dosage,dosageregimen,andtreatment period(s).

Astatementthatthetrialwillbeconductedincompliancewiththeprotocol,GCPandtheapplicable regulatory requirement(s).

Descriptionofthepopulationtobestudied.

Referencestoliteratureanddatathatarerelevanttothetrial, andthatprovidebackgroundforthetrial.

3. TrialObjectivesandPurpose-Adetaileddescriptionoftheobjectivesandthepurposeofthetrial.

4. TrialDesign-Thescientificintegrityofthetrialandthecredibilityofthedatafromthetrialdepend substantially on the trial design.

Adescription ofthetrialdesignshouldinclude:

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

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.

Adescriptionofthemeasurestakentominimize/avoidbias,including:

(a) Randomization.

(b) Blinding.

Adescription of the trialtreatment(s) andthe dosageand dosageregimen of the investigationalproduct(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

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

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

Accountabilityproceduresfor theinvestigationalproduct(s), includingtheplacebo(s)andcomparator(s),if any.

Maintenanceoftrialtreatmentrandomizationcodes andproceduresforbreakingcodes.

Theidentificationofany data toberecorded directlyontheCRFs (i.e. noprior written or electronicrecord of data), and to be considered to be source data.

5. SelectionandWithdrawalofSubjects -

Subjectinclusioncriteria.

Subjectexclusioncriteria.

Subjectwithdrawalcriteria(i.e.terminatinginvestigationalproducttreatment/trialtreatment)and procedures specifying:

(a) Whenandhowtowithdrawsubjectsfromthetrial/ investigationalproduct treatment.

(b) Thetypeandtimingofthedatatobecollectedforwithdrawnsubjects.

(c) Whetherandhowsubjects aretobereplaced.

(d) Thefollow-upfor subjectswithdrawnfrominvestigationalproducttreatment/trialtreatment.

6. TreatmentofSubjects-

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-upperiod(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

Medication(s)/treatment(s)permitted(includingrescuemedication)andnotpermittedbeforeand/or during the trial.

Proceduresformonitoringsubjectcompliance.

7. AssessmentofEfficacy-

Specificationoftheefficacyparameters.

Methodsandtimingforassessing,recording,andanalysingofefficacyparameters.

8. AssessmentofSafety-

Specificationofsafetyparameters.

Themethodsandtimingforassessing,recording,andanalysingsafetyparameters.

Proceduresforelicitingreportsofandforrecordingandreportingadverseeventandintercurrent illnesses.

Thetypeanddurationofthefollow-upofsubjectsafteradverseevents.

9. Statistics-

Adescriptionofthestatisticalmethodstobeemployed,includingtimingofanyplannedinterimanalysis.

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.

Thelevelofsignificancetobeused.

Criteriafortheterminationofthetrial.

Procedureforaccountingformissing,unused,andspuriousdata.

Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should bedescribed and justified in protocol and/or in the final report, asappropriate).

Theselectionofsubjects tobeincluded intheanalyses (e.g. allrandomizedsubjects, alldosedsubjects, all eligible subjects, evaluable subjects).

10. DirectAccesstoSourceData/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. QualityControlandQualityAssurance

12. Ethics-Descriptionofethicalconsiderationsrelatingtothetrial.

13. DataHandlingandRecordKeeping

14. FinancingandInsurance-Financingandinsuranceifnotaddressedina separateagreement.

15. PublicationPolicy-Publicationpolicy,ifnotaddressedinaseparateagreement.

16. Supplements

O<u>BiostatisticsinPharmaceuticalProductDevelopment-</u>

Statisticsplaysanimportantroleindrugproductdevelopment.Itsuseisnecessaryforplanningandanalyzing trialsandusingstatistics correctlyis crucialfor thesuccess of drugdevelopment programs. Applications of biostatistics in pharmaceutical product development are as follows –

- Providescientific methodthinkingintothetargetidentificationprocess
- AssesstheabilitytoQuantifyeffectontargetofinterest

  -Doesanimalmodeltranslateinto human?

  -Howwill effectivedosebeidentified?
- Providecriticalinputintoquantificationofrisk(Riskassessment)
- Agreecriteriafor stoppingdoseescalation
- Assistinestablishinggo/nogodecisioncriteria(significancetesting-pvalue)
- Reviewofsafetymarginsfromanimal data
- Assistinappropriatestudydesignselectionandof Primaryendpointsforstudies.
- Designandimplementationofrandomizationsystemsin studydesign.
- Helpsinsamplecollection, dataanalysisandrefinement, errorandbias detection.
- Designandoptimizeformulation,optimizeprocessparametersinpilotplantscaleup.
- UsedasAnalyticalmethodsvalidationtool.

KeyStatisticalsupportsindifferentphasesofdrugdevelopmentaresummarizebelow–

Table4-DrugProductDevelopmentandStatisticalSupport

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)
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. **TEXTEXPOSITION–**

A. Content - Most NDA submissions contain an enormous amount of data, which cannot be presented entirely within thebody 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 aspecifictheSis shouldbepresented withinthebodyofthedocument rather thanplaced intoa remoteappendix, which will impede the review.

Less important data can besummarized 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 theapplication. 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-ThefollowingpointsaddresswaysOf makingNDAdocumentsmoreconcise.

1. Keepthelanguagesimpleandstraightforward.

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. Eliminateredundancies. Acarefulreviewofthetext willfind manywords, 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 thescientific 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. Sentencestructureandlength.

3. Misplacedmodifiers.

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 upautomatically 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 appropriateheaders toidentifythesection. Multipleandsequentialindentingwastes **of**spaceandis confusing. Short lists are appropriately indented, and conventions like indenting with bullets are useful to break up long sections of text.

I. GlobaltoSpecific-

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 byseverity, 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. **TABULARPRESENTATION-**

In-text, tables should be used whenever they simplify the presentation and allow for substantial reduction in text. Comprehensivemultipagetables that interrupt text shouldbeavoided, ifpossible, unless theyarecritical. However,if the tables are very important,they can be placed in the same volumein 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 precedethetable, beginning withan introductiontothetablebynumber anda statement identifying what type of data it contains.

Additionalcommentaryrelatedtothetablebutnot derivedfromthetabulardatamayfollowthetable.

A. Title-Alltablesrequireconcisebutdescriptivetitles.

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 intoseparatesections under thesamecolumn headers, with descriptive headings for eachsectionspanningthe 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, theelderly, racialsubgroups,impairedrenalfunction)inthesamecolumnineachtable.

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.

OManagementofClinicalTrials–Thekeyelementsinmanagingclinicalprogramsareasfollows-.

* **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 andSource 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 monitorthe 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 GCPregulations and guidelines andadheretotheprotocoltoassurethat therights ofthesubjects 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 theclinical trial? What kind of medical treatment arethey presently receiving, and who arethey 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.Thesponsor is responsiblefor retrieving/verifying thedisposition 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 requirea sponsor toreport adverse experiences andreactions for aninvestigationalproduct atboth the investigational and the post marketing stages.

*Financialdisclosure- Oneof thenewest components of a clinicaltrialisfinancialdisclosure. This regulation initiated in the United States on February 2, 1999, is required on all current orongoingclinical 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 paymentsofother sortstotheinvestigator or institution(e.g., equipment, honorariums). Thereason 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 appropriatelyclosed. This cannot occur until all of the subjects havecompletedthecourseof thetrial, 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:

Allsubjects enteredinthetrialhavebeenaccounted for.

AllCRFpageshavebeencompletedandretrieved. All

data queries have been resolved.

AllAEsandADRshavebeenreportedandfollowed up.

Allinvestigationalproducthasbeenaccountedfor anddisposedofor returnedtothesponsor. All

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

RegulatoryrecordsarecompleteandorganizedintheTrialBinder. All

outstanding issues are addressed.

* **Records retention and inspections -** Record retention is critical to the ongoing viability of the study data. TheFDAor other healthcareauthorities mayconduct anon-siteinspectiontoverifythedata froma givensite at some time after submission of the New Drug Application (NDA). This information must be readilyavailableat thesite. Both theCFR and theICHrequire that therecords beretained for two years after thedate of a marketing application is approved.

ListofAbbreviations:

ADME-Absorption,distribution,metabolism,excretion ADR
– Adverse Drug Reaction
AUC-Area underthecurve
ANDA-AbbreviatedNewDrugApplication(foragenericdrug) DoE –
Design of Experiment
CFR-*CodeofFederal Regulations*(usuallycitedbypartandchapter, as 21CFR211) EU-
European Union
GCP- Good Clinical Practice
GLP-GoodLaboratoryPractice IB
- Investigator's Brochure
ICH-InternationalConferenceonHarmonizationofTechnicalRequirementsfor Registrationof Pharmaceuticals for Human Use
IEC-IndependentEthicsCommittee
IND-InvestigationalNewDrugApplication
IRB-InstitutionalReviewBoard,sometimesIndependentReviewBoard. IRC -
Institutes Review Committee
IRD-InternationalRegistrationDocument
ISO-InternationalOrganisationforStandardisation
MAA -Marketing Authorization Application
MTD-Maximumtoleratеddose
NCE - New chemical entity
NDA- New Drug Application
PAT-ProcessAnalyticalTechnology SPC
– Statistical Process Control
USFDA-U.S.FederalDrugAdministration

References -

1. GuarinoRA:NewDrugApprovalProcess: AcceleratingGlobalRegistrations. 4th ed.:MarcelDekker, Inc. (New York), 2004.

2. SennS:StatisticalIssuesinDrugDevelopment,2nded.:©JohnWiley&Sons, Ltd, (WestSussex)2007.

3. Turner JR:NewDrugDevelopment:Design, MethodologyandAnalysis. ©JohnWiley& Sons, Ltd, (West Sussex) 2007.

4. Pattersons, JonesB.:BioequivalenceandStatisticsInClinicalPharmacology. ©Chapman&Hall/CRC, 2006.

5. ChowSC,ShaoJ.:StatisticsInDrugResearch:Methodologies AndRecentDevelopments. MarcelDekker, Inc. (New York), 2002.

6. Chapter 12: Regulatory Affairs: Moyer, E. D.:Keeping Product Development on Track. In: Cynthia Robbins-Roth,editors. AlternativeCareersinScience.2nded.:AcademicPress;©2006ElsevierInc.p. *125– 138*.

7. RoshanK, Jha A.:RoleOfRegulatoryAffairsInPharmaceuticalCompany:AnOverview. GlobalJournal for Research Analysis 2008; 7(1): *51-53*.

8. SanghiDK,TiwleR.:RoleofRegulatoryAffairsinaPharmaceuticalIndustry. InternationalJournalof Pharmacy Review & Research 2014; 4 (2): *127-131*.

9. SawantAM, MaliDP,BhagwatDA. :RegulatoryRequirementsandDrugApprovalProcessinIndia, Europe and US. Pharmaceutical Regulatory Affairs 2018; 7 (2): *1-10*.

10. PetersonJJ,SneeRD,McAllister PR,SchofieldTL,Carella AJ. :StatisticsinPharmaceutical Development and Manufacturing. Journal of Quality Technology 2009; 41 (2): *111-134*.

11. AndradeE.L, Bento A, Cavalli J, Oliveira SK, SchwankeR.C, Siqueira J.M, Freitas C.S, Marcon R, J.B. Calixto. : Non clinical studies in the process of new drug development – Part II: Good laboratory practice, metabolism, pharmacokinetics, safetyanddosetranslationtoclinicalstudies. BrazilianJournalofMedicaland Biological Research 2016; 49(12): *1-19*.

12. DoratoMA,BuckleyLA. :ToxicologyintheDrugDiscoveryandDevelopmentProcess.Current Protocols in Pharmacology 2006; 32 (1): *10.3.1-10.3.35*.

13. PatravaleVB,DisouzJI,RustomjeeM.:PharmaceuticalProductDevelopment:InsightsInto PharmaceuticalProcesses,ManagementandRegulatoryAffairs.1sted.:©CRCPress,2016.

14. E6(R2)GoodClinicalPractice:IntegratedAddendumtoICHE6(R1)-GuidanceforIndustry

15. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

16. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials

17. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization

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