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**A TEXT BOOK OF**  
**PHARMACEUTICAL**  
**REGULATORY SCIENCE**  
**FOR B.PHARMACY FINAL YEAR**  
**(As per PCI Syllabus)**

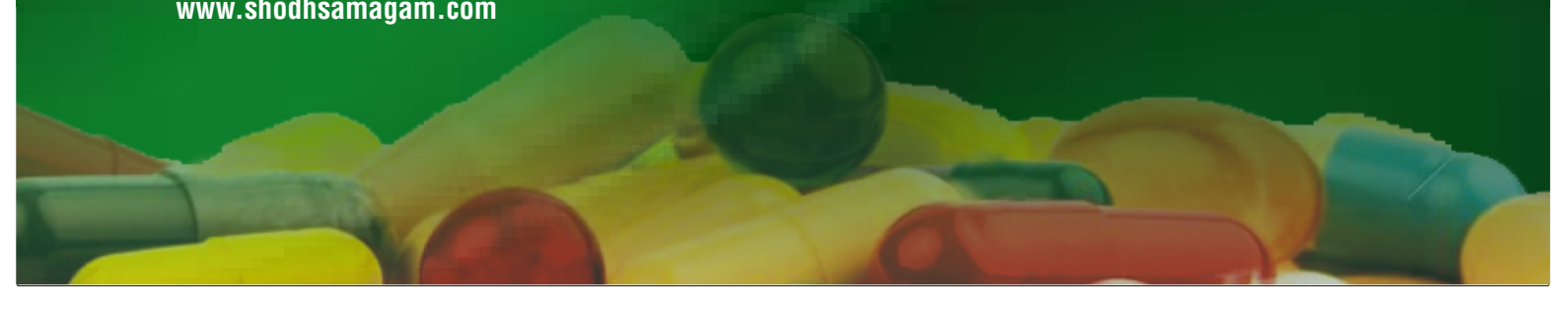


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Dr. B. E Wanjari, K. K. Khalode,  
K. B. Bhendarkar, M. N. Rangari

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# PHARMACEUTICAL REGULATORY SCIENCE

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# PHARMACEUTICAL REGULATORY SCIENCE

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## Preface

Regulatory Affairs is a comparatively new profession which has 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, agrochemical, cosmetics and complementary. In present edition, all the possible efforts has been made to incorporate all the data available on pharmaceutical regulatory affairs science.

Very few books are available on this subject, the material in most of the books is presented in diffused form or is highly specialized and discernible to those proficient in the field. The main objective of writing this book is to present the information as per the pharmacy council of India syllabus designed for eighth semester of B. Pharmacy.

This book consist of five units. Almost each unit contain one to two chapters. Chapter one of unit one includes, New Drug Discovery and development. The unit two consist of two chapters including Regulatory Approval Process and Regulatory authorities and agencies. Unit three is Registration of Indian drug product in overseas market. Unit four consist of two chapters Clinical trials and lastly unit 5 consist of one chapter Regulatory Concepts.

The constructive suggestion for further improvements from teachers and students are welcome.

**Gondia**

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**CHAPTER 01**



**New Drug Discovery and development**

**Stages of drug discovery**

**Drug development process**

**Pre-clinical studies**

**Non-clinical activities**

**Clinical studies**

**Innovator and generics**

**Concept of generics**

**Generic drug product development.**





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## Background

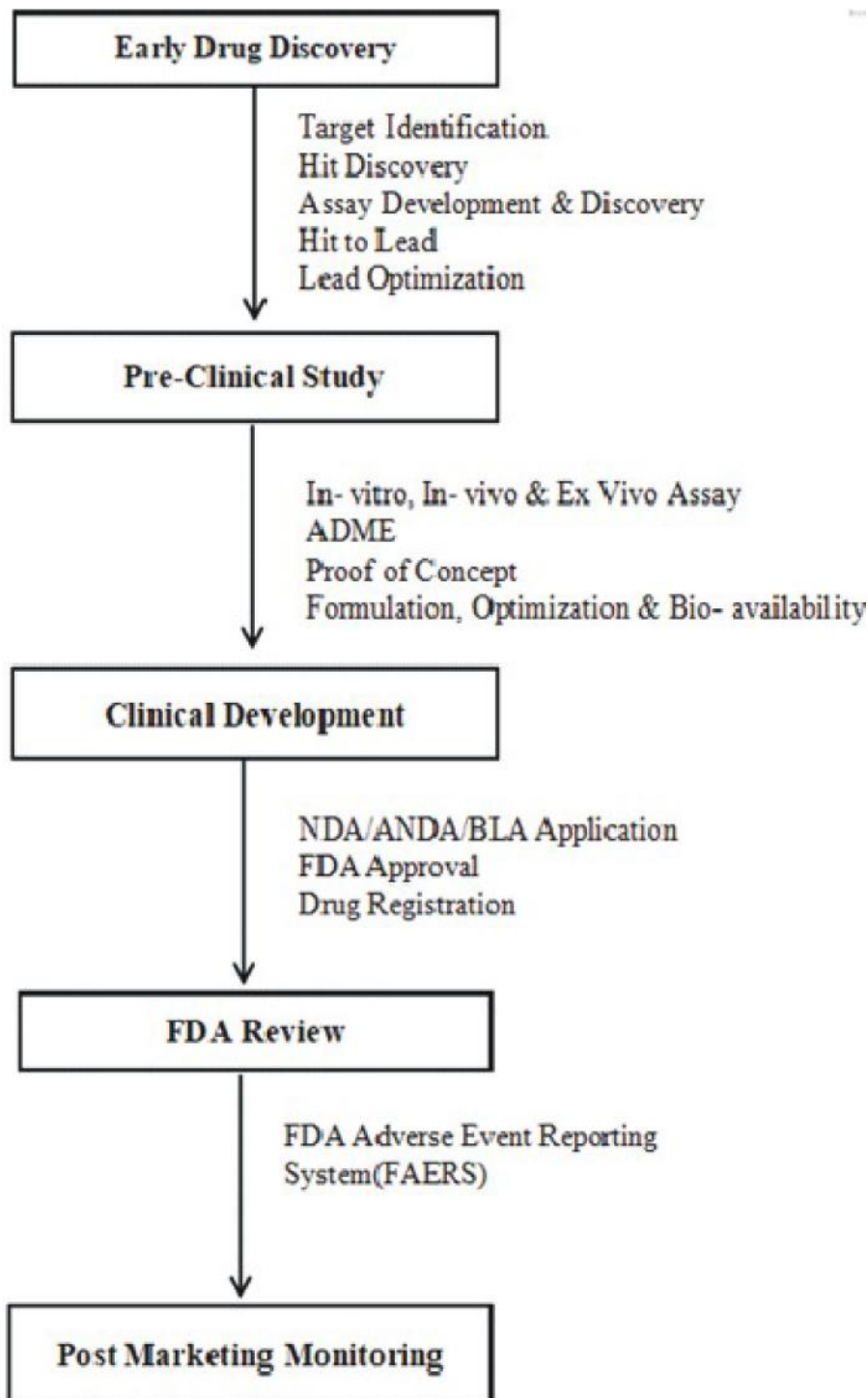
Drug discovery is multifaceted process which involved identification of a drug chemicals to find out therapeutic use in treating and management of various disease conditions.

The drug discovery process of drug includes identification of drug candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. When a molecule avails its satisfactory results in these investigations, it will commence the process of drug development subsequent to clinical trials. Drug discovery and development is an expensive process due to the high budgets of R&D and clinical trials. It takes almost 12-15 years to develop a single new drug molecule from the time it is discovered when it is available in market for treating patients. The average cost for research and development for each efficacious drug is likely to be \$900 million to \$2 billion. This figure includes the cost of the thousands of failures: For every 5,000-10,000 compounds that enter the investigation and development pipeline, ultimately only one attains approval. These statistics challenge imagination, but a brief understanding of the R&D process can explain why so many compounds don't make it and why it takes such a large, lengthy effort to get one medicine to patients. The Success requires immense resources the best scientific and logical minds, highly sophisticated laboratory and technology; and multifaceted project management. It also takes persistence and good fortune. Eventually, the process of drug discovery brings hope, faith and relief to billions of patients.

## Stages of Drug Discovery and Development Process

Across the pharmaceutical industry there are several mandated processes that must be undergone before the final sale of a drug can begin on the market. Following are the different stages which are required to get approval of new drug for market authorization from Food and Drug Administration (FDA).

1. Targetidentification
2. Targetvalidation
3. lead identification
4. lead optimization
5. Product characterization
6. Formulation and development
7. Pre- clinical research
8. Investigational New Drug
9. Clinicaltrials
10. New Drug Application & Approval



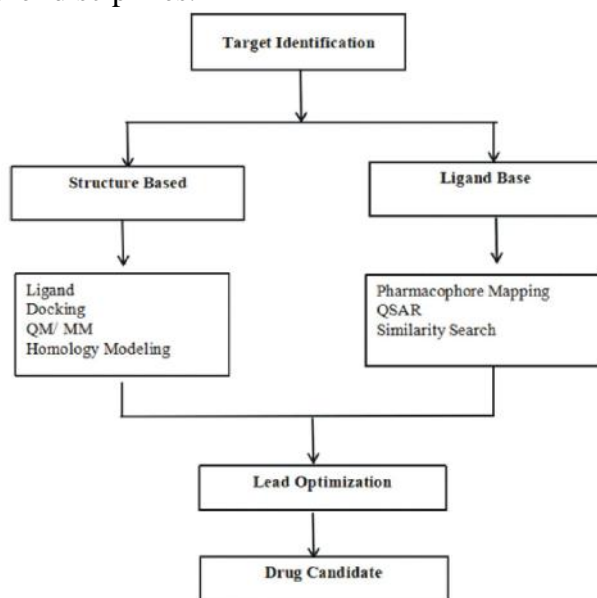
**Figure 1:** Stages of drug discovery and development process

## 1. Target Identification

Every year thousands of molecule discover through high- throughput screening which leads to identify target. By interaction with target, potential drug is assessed. Lead compounds are further screened after assessment and then screened for their properties and activities to develop safe and effective medicine.

The first step in the discovery of a drug is identification of the biological origin of a disease, and the potential targets for intervention. Target identification starts with isolating the function of a possible

therapeutic target (gene/nucleic acid/protein) and its role in the disease. [6] Identification of the target is followed by characterization of the molecular mechanisms addressed by the target. An ideal target should be efficacious, safe, meet clinical and commercial requirements and be druggable'. The techniques used for target identification may be based on principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines.



**Figure 2:** Target Identification

## Approaches

- i. Data mining using bio-informatics
- ii. Identifying, selecting and prioritizing potential disease targets
- iii. Genetic association
- iv. Genetic polymorphism and connection with the disease
- v. Expression profile
- vi. Changes in mRNA/protein levels
- vii. Pathway and phenotypic analysis- In vitro cell-based mechanistic studies
- viii. Functional screening
- ix. knockdown, knockout or using target specific tools

## 2. Target Validation

Target validation is the process by which the expected molecular target – for example gene, protein or nucleic acid of a small molecule is certified. Target validation includes: determining the structure activity relationship (SAR) of analogs of the small molecule; generating a drug-resistant mutant of the presumed target; knockdown or over expression of the presumed target; and monitoring the known signaling systems downstream of the presumed target.

Target validation is the process of demonstrating the functional role of the identified target in the disease phenotype. Whilst the validation of a drug's efficacy and toxicity in numerous disease-relevant cell models and animal models is extremely valuable – the ultimate test is whether the drug works in a clinical setting.



**Figure 3 : Target Validation**

Target validation can be broken down in to two key steps.

**i. Reproducibility**

Once a drug target is identified, whether it be via a specific technique or from review of literature, the first step is to repeat the experiment to confirm that it can be successfully reproduced. The target validation technique includes affinity chromatography, expression-cloning, protein micro-array, reverse transected cell micro-array, biochemical suppression, siRNA, DNA micro-array, system biology and study of existing drugs.

**ii. Introduce variation to the ligand (drug)-target- environment**

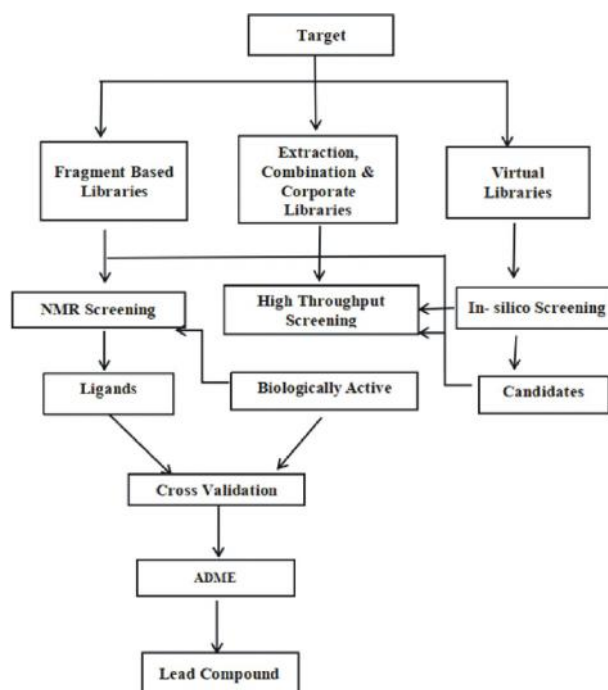
Genetic manipulation of target genes (in vitro) knocking down the gene (shRNA, siRNA, miRNA), knocking out the gene (CRISPR), knocking in the genes (viral transfection of mutant genes) Antibodies, interacting to the target with high affinity and blocking further interactions, Chemical genomics, chemical approaches against genome encoding protein.

**3. Identification of Lead**

A chemical lead is defined as a synthetically stable, feasible, and drug like molecule active in primary and secondary assays with acceptable specificity, affinity and selectivity for the target receptor. This requires definition of the structure activity relationship as well as determination of synthetic feasibility and preliminary evidence of in vivo efficacy and target engagement. It is also called as developmental candidate. Characteristics of a chemical lead are:

- i. SARdefined
- ii. Drug ability (preliminary toxicity, hERG)
- iii. Synthetic feasibility
- iv. Select mechanistic assays
- v. In vitro assessment of drug resistance and efflux potential
- vi. Evidence of in vivo efficacy of chemical class
- vii. PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies

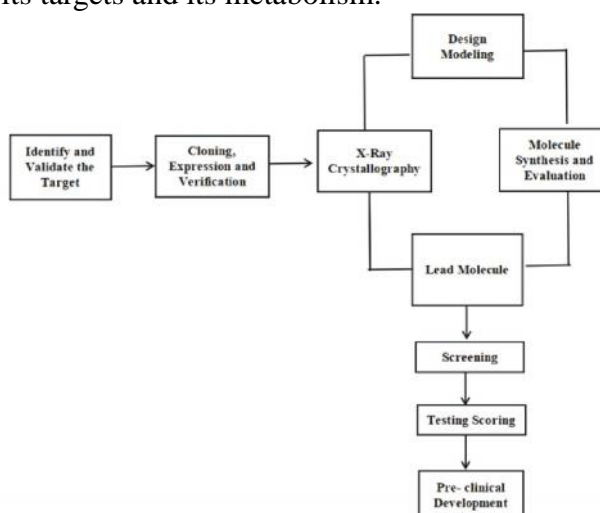
In order to decrease the number of compounds that fail in the drug development process, a drug ability assessment is often conducted. This assessment is important in transforming a compound from a lead molecule into a drug. For a compound to be considered druggable it should have the potential to bind to a specific target; however, also important is the compound’s pharmacokinetic profile regarding absorption, distribution, metabolism, and excretion. Other assays will evaluate the potential toxicity of the compound in screens such as the Ames test and cytotoxicity assay.



**Figure 4 : Lead Identification**

#### 4. Lead Optimization

Lead optimization is the process by which a drug candidate is designed after an initial lead compound is identified. The process involves iterative series of synthesis and characterization of a potential drug to build up a representation of in what way chemical structure and activity are related in terms of interactions with its targets and its metabolism.



**Figure 5 : Lead Optimization**

In initial drug discovery, the resulting leads from hit-to-lead high throughput screening tests undergo lead optimization, to identify promising compounds. Potential leads are evaluated for a range of properties, including selectivity and binding mechanisms during lead optimization, as the final step in early stage drug discovery. The purpose of lead optimization is to maintain favorable properties in lead compounds, while improving on deficiencies in lead structure. In order to produce a pre-clinical drug candidate, the chemical structures of lead compounds (small molecules or biologics) need to be altered to improve target specificity and selectivity. Pharmacodynamic and pharmacokinetic parameters and toxicological properties are also evaluated. Labs must acquire data on the toxicity, efficacy, stability

and bio-availability of leads, in order to accurately characterize the compound and establish the route of optimization.

Researchers in drug discovery need rapid methods to narrow down the selection of drug candidates for this downstream selectivity profiling and further investigation. High throughput DMPK (drug metabolism and pharmacokinetics) screens have become an essential part of lead optimization, facilitating the understanding and prediction of in vivo pharmacokinetics using in vitro tests. In order to make new drugs with higher potency and safety profiles, chemical modifications to the structure of candidate drugs are made through optimization. Automated screening systems are becoming an important part of pharmaceutical and bio-pharmaceutical drug discovery labs. Mass spectrometry is used for the detection and quantitation of metabolites. MALDI imaging is a key technique for evaluating drug candidates and their metabolites in tissue structure rapidly and accurately. Additionally, NMR Fragment-based Screening (FBS) in the pharmaceutical industry has become a widely applied method for the discovery and optimization of lead molecules in targeted screening campaigns.

## **5. Product Characterization**

When any new drug molecule shows a promising therapeutic activity, then the molecule is characterized by its size, shape, strength, weakness, use, toxicity, and biological activity. Early stages of pharmacological studies are helpful to characterize the mechanism of action of the compound.

## **6. Formulation and Development**

Pharmaceutical formulation is a stage of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized to produce a bio-available, stable and optimal dosage form for a specific administration route.

During pre-formulation studies the following parameters are evaluated:

- Solubility in different media and solvents
- Dissolution of the active pharmaceutical ingredient(API)
- Accelerated Stability Services under various conditions
- Solid state properties (polymorphs, particle size, particle shape etc.)
- Formulation services and capabilities
- Formulation development of new chemical entities(NCE)
- Optimization of existing formulations
- Process development for selected dosage forms
- Novel formulations for improved delivery of existing dosage forms
- Controlled release and sustained release formulations
- Self-emulsifying drug delivery systems
- Colloidal drug delivery systems
- Sub-micron and nano-emulsions

## **7. Pre- clinical Testing**

Pre-clinical research in drug development process involves evaluation of drug's safety and efficacy in animal species that conclude to prospective human outcome. The pre- clinical trials also have to acquire approval by corresponding regulatory authorities. The regulatory authorities must ensure that trials are conducted in safe and ethical way and would give approval for only those drugs which are confirm to be safe and effective. ICH has established a basic guideline for technical necessities of acceptable preclinical drug development.

The pre-clinical trials can be conducted in two ways: General pharmacology and Toxicology. Pharmacology deals with the pharmacokinetic and pharmacodynamic parameters of drug. It is essential to explore unwanted pharmacological effects in suitable animal models and monitoring them in toxicological studies. Pharmacokinetic studies are very important to make known the safety and efficacy parameters in terms of absorption, distribution, metabolism and excretion. These studies give information on absorption rate for diverse routes of administration, which helps in selection of dosage form, distribution, rate of metabolism and elimination; which governs the half-life of the drug. Half-life of the drug clarifies the safety outline of the drug which is the obligatory for a drug to get approved by regulatory agencies. The drug distribution mechanism elucidates the therapeutic effectiveness of the drug as it depends on the drug's bio-availability and its affinity. Drug metabolism provides the probability of through phases of bio-transformation process and formation of drug metabolites. It also helps in understanding the reactions as well as enzymes involved in bio-transformation.

Toxicological studies of the drug can be performed by in- vitro and in-vivo test which evaluate the toxicological effects of the drug. In-vitro studies can be performed to inspect the direct effects on cell proliferation and phenotype. In-vivo studies can be performed for qualitative and quantitative determination of toxicological effects. As many drugs are species specific, it is essential to select appropriate animal species for toxicity study. In-vivo studies to evaluate pharmacological and toxicological actions, including mode of action, are often used to support the basis of the proposed use of the product in clinical studies.

## **8. The Investigational New Drug Process (IND)**

Drug developers must file an Investigational New Drug application to FDA before commencement clinical research. In the IND application, developers must include:

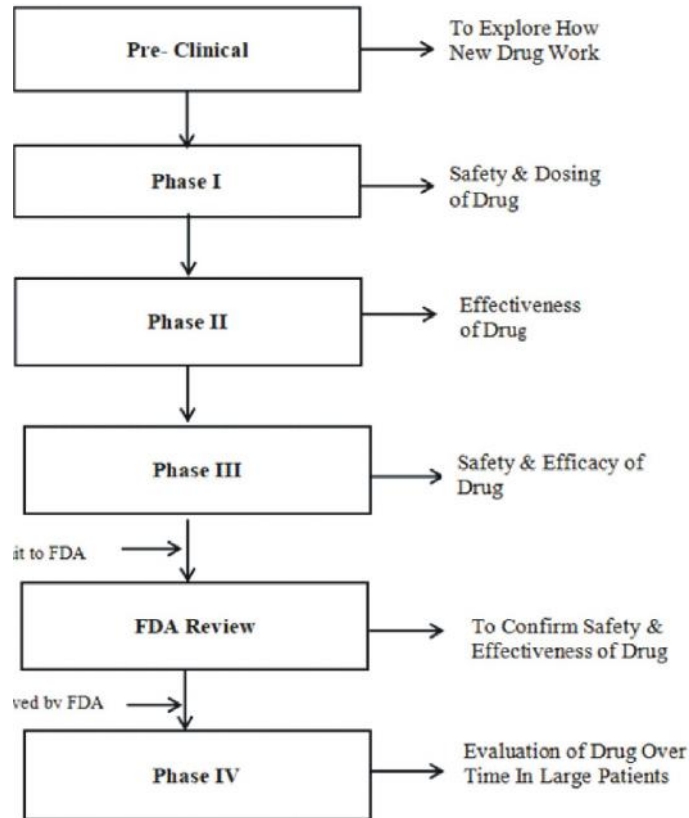
- Preclinical and toxicity study data
- Drug manufacturing information
- Clinical research protocols for studies to be conducted
- Previous clinical research data (if any)
- Information about the investigator/developer

## **9. Clinical Research**

Clinical trials are conducted in people (volunteer) and intended to answer specific questions about the safety and efficacy of drugs, vaccines, other therapies, or new methods of using current treatments. Clinical trials follow a specific study protocol that is designed by the researcher or investigator or manufacturer. As the developers design the clinical study, they will consider what they want to complete for each of the different Clinical Research Phases and starts the Investigational New Drug Process (IND), a process they must go through before clinical research begins. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:

- Selection criteria for participants
- Number of people take part of the study
- Duration of study
- Dose and route of administration of dosage form
- Assessment of parameters
- Data collection and analysis





**Figure 6 :** Phases of clinical trials

**i. Phase 0- clinical trial**

Implicates investigative, first-in-human (FIH) trials that are conducted according to FDA guidelines. Phase 0 trials besides termed as human micro dose studies, they have single sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging specific targets without exerting pharmacological actions. Pharmaceutical industries perform Phase 0 studies to pick which of their drug applicants has the preeminent pharmacokinetic parameters in humans.

**ii. Phase 1- Safety and dosage**

Phase I trials are the first tests of a drug with a lesser number of healthy human volunteers. In most cases, 20 to 80 healthy volunteers with the disease/condition participate in Phase 1. Patients are generally only used if the mechanism of action of a drug indicates that it will not be tolerated in healthy people. However, if a new drug is proposed for use in diabetes patients, researchers conduct Phase 1 trials in patients with that type of diabetes. Phase 1 studies are closely monitored and collect information about Pharma codynamics in the human body. Researchers adjust dosage regimen based on animal study data to find out what dose of a drug can tolerate the body and what are its acute side effects. As a Phase 1 trial continues, researchers find out research mechanism of action, the side effects accompanying with increase in dosage, and information about effectiveness. This is imperative to the design of Phase 2 studies. Almost 70% of drugs travel to the next phase.

**iii. Phase 2- Efficacy and side effects**

Phase II trials are conducted on larger groups of patients (few hundreds) and are aimed to evaluate the efficacy of the drug and to endure the Phase I safety assessments. These trials aren't sufficient to confirm whether the drug will be therapeutic. Phase 2 studies provide with additional safety data to the researchers. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols. Around 33% of drugs travel to the next phase.

Most prominently, Phase II clinical studies aid to found therapeutic doses for the large-scale Phase III studies.

#### **iv. Phase 3- Efficacy and adverse drug reactions monitoring**

Researchers plan Phase 3 studies to prove whether a product deals an action benefit to a specific people or not. Sometimes known as pivotal studies, these studies comprise 300 to 3,000 volunteers. Phase 3 studies deliver most of the safety data. The previous study might not able to detect less common side effects. But phase 3 studies are conducted on large no. of volunteers and longer in duration, the results are more probable to detect long-term or uncommon side effects. Around 25-30% of drugs travel to the next phase of clinical research.

If a drug developer has data from its previous tests, preclinical and clinical trials that a drug is safe and effective for its intended use, then the industry can file an application to market the medicine. The FDA review team comprehensively inspects all submitted data on the drug and makes a conclusion to approve or not to approve it. New Drug Application

A New Drug Application (NDA) expresses the full story of a drug molecule. Its purpose is to verify that a drug is safe and effective for its proposed use in the people studied. A drug developer must include all about a drug starting from pre- clinical data to Phase 3 trial data in the NDA. Developers must include reports on all studies, data, and analysis. Beside with clinical trial outcomes, developers must include:

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information Institutional review board compliance information
- Directions for use

#### **v. FDA Review**

Once FDA obtains a complete NDA then FDA team of review may require about 6 to 10 months to take a pronouncement on whether to approve the NDA. If Once FDA obtains an incomplete NDA then FDA team of review refuse the NDA.

If FDA governs that a drug has been revealed to be safe and effective for its proposed use, it is then essential to work with the developer for upgrade prescribing information. This is denoted as labeling. Labeling precisely defines the basis for approval and direction how to use the drug. Although, remaining issues required to be fixed before the drug to be approved for marketing. In other cases, FDA have need of additional studies. At this situation, the developer can choose whether to continue further development or not. If a developer distresses with an FDA decision, there are tools for official appeal.

#### **vi. Phase 4- Post-Market Drug Safety Monitoring**

Phase 4 trials are conducted when the drug or device has been approved by FDA. These trials are also recognized as post- marketing surveillance involving pharmacovigilance and continuing technical support after approval. There are numerous observational strategies and assessment patterns used in Phase 4 trials to evaluate the efficacy, cost- effectiveness, and safety of an involvement in real-world settings. Phase IV studies may be required by regulatory authorities (e.g. change in labelling, risk management/minimization action plan) or may be undertaken by the sponsoring company for competitive purposes or other reasons. Therefore, the true illustration of a drug 's safety essentially requires over the months and even years that mark up a drug 's lifespan in the market. FDA reviews reports of complications with prescription and OTC drugs, and can decide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions.

## **10. A New Drug Application and Approval**

A new drug application (NDA) is a comprehensive document that must be submitted to the U.S. Food and Drug Administration (FDA) in order to request approval for marketing a new drug in the United States.

The new drug approval is of two phase process - the first phase for clinical trials and second phase for marketing authorization of drug. Firstly, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. Thereafter, the clinical trials can be conducted (phase I to phase IV). These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings. After the completion of clinical studies of the drug, then an application to the competent authority of the concerned country for the approval of drug for marketing is submitted. The competent authority review the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect .

Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research trial and its adverse effects (in particular populations), should also be monitored.

### **Innovator and Generics**

#### **Drug**

Any substance or pharmaceutical product for human use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient

#### **Innovator product**

The innovator product is generally that which was first authorized for marketing (normally as a patented product)

When a substance has been available for many years, it may not be possible to identify an innovator pharmaceutical product

#### **Generic drug**

A pharmaceutical product, usually intended to be interchangeable with the innovator product, marketed after expiry of the patent or other exclusivity rights.

Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name.

They may be marketed in dosage forms and/or strengths different from those of the innovator products

### **Concept of Generics and Generic Drug Product Development**

#### **Definitions of Generics**

Confusion often surrounds terms used in the global field of generics and biosimilars.

The source of some of this confusion is due to authorities in various regions of the world defining terms differently and other instances due to a misunderstanding of the actual nature, characteristics, and method of research and manufacture of generic and biological products.

In an attempt to improve public understanding and avoid confusion, GaBI Online has decided to provide tables of definitions used in different countries or regions. Table 1 shows a glossary of the relevant terms for biosimilars as defined by WHO.

## **WHO Definitions Relevant to Generics**

### **Active pharmaceutical ingredient (API)**

The chemical substance responsible for a product's effect. In this manual, it is called 'substance'.

### **Bioequivalence**

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

### **Brand name**

Name given to a pharmaceutical product by the manufacturer, e.g. Valium is the originator brand name (also called trade name) for diazepam. The use of this name is reserved exclusively to its owner as opposed to the generic name, i.e. diazepam. Brand names may also be used for generic products; they are then often called 'branded generics'. These brand names are different from innovator brand names. See generic medicine.

### **Comparator**

The term 'comparator' is used to mean 'the pharmaceutical product with which the new product is intended to be interchangeable in clinical practice'. In any particular market, the comparator should be the first in this list that is available:

- The product for which efficacy, safety and quality have been fully established (often the innovator)
- A market leader that has been authorized for marketing after a process of assessment a market leader that is legally marketed but has not been assessed prior to marketing authorization.

### **Dispensing fee**

Normally a fixed fee that pharmacies are allowed to charge per prescribed item instead of, or in addition to a percentage mark-up. The fee more accurately reflects the work involved in dispensing a prescription; a percentage mark-up makes profit dependent on the sale of expensive medicines.

### **Dosage form**

The administration form of the completed pharmaceutical product, e.g. tablet, capsule, suspension, injection. Also called 'dose form' or 'dosing unit'

### **Drug**

Any dosage form containing a substance approved for the prevention and treatment of disease. The term 'medicine' is increasingly used to distinguish it from a drug as a substance that is misused. See also Pharmaceutical product

### **Essential medicines**

Essential medicines are intended to be available within the context of functioning health systems at all times, in adequate quantities, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and community can afford. The WHO model list of essential medicines is intended to be flexible and adaptable to many different situations; the precise definition of the medicines that are regarded as essential remains a national responsibility.

### **Excipient**

Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.

### **Finished product**

A product that has undergone all stages of production, including packaging in its final container and labelling.

### **Formulatio**

The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

### **Generic medicine/ Multi-source product**

A pharmaceutical product usually intended to be interchangeable with the originator brand product, manufactured without a license from the originator manufacturer and marketed after the expiry of patent or other exclusivity rights.

Generic medicines are marketed either under a non-proprietary name, for example diazepam or occasionally another approved name, rather than under a proprietary or brand name. However, they are also quite frequently marketed under brand names, often called 'branded generics'. Many different branded generic products of the same medicine can be on the market in a country along with the originator brand product.

The manual 'Marketing Authorization of Pharmaceutical Products with Special Reference to Multi-source (Generic) Products (WHO/DMP/RGS/98.5)' defines and uses the term 'multi-source pharmaceutical product' for generic products. This includes even an originator brand for which the patent has expired. This definition of a generic is used in some countries, but the manual distinguishes between originator brand, regardless of its patent status, and lowest-priced generic equivalents.

### **Innovator brand**

#### **International non-proprietary name (INN)**

A common, generic name selected by designated experts for the unambiguous identification of a new pharmaceutical substance. The selection process is based on a procedure and guiding principles adopted by the World Health Assembly. INNs are recommended for worldwide use.

The system was introduced by WHO in 1950 as a means of identifying each pharmaceutical substance or active pharmaceutical ingredient by a unique name that is universally accessible as public property (non-proprietary). It is often identical to the generic name, e.g. diazepam. A brand name (trade name) should not be derived from the INN name.

#### **Interchangeable pharmaceutical products**

Products within a therapeutic class but with different active ingredients are interchangeable if they have equivalent therapeutic effect.

### **Medicine**

Any dosage form containing a substance approved for the prevention and treatment of disease. The term 'medicine' is increasingly used to distinguish it from a drug as a substance that is misused. See also Pharmaceutical product

#### **Originator pharmaceutical product/originator brand**

Generally the product that was first authorized worldwide for marketing, normally as a patented product, on the basis of the documentation of its efficacy, safety and quality, according to requirements at the time of authorization, e.g. Valium. The originator product always has a brand name; this name may, however, vary between countries.

Some substances (e.g. prednisolone and isoniazid) are so old that no originator can be identified and the patent was probably never claimed.

### **Patent**

A title granted by public authorities that confers a temporary monopoly for the exploitation of an invention upon the person who reveals it, furnishes a sufficiently clear and full description of it, and claims this monopoly.

**Patient co-payments**

Payments by patients of a fixed amount per prescribed medicine, even if reimbursed.

**Pharmaceutical equivalence**

Medicines with identical amounts of the same active ingredient in the same dosage form and route of administration that meet the standards of strength, quality, purity and identity.

**Pharmaceutical product**

Any medicine intended for human use, presented in its finished dosage form that is subject to control by pharmaceutical legislation (registered). A product may be sold under a brand name (e.g. Valium) or under the generic name (e.g. diazepam).

**Substance**

See active pharmaceutical ingredient.

**Stability**

The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf life. The chemical, physical, microbiological and bio-pharmaceutical aspects of stability must be considered.

**Trade name**

See brand name.

## **Generic Drug Product Development**

**Background**

The drug which have same chemical composition as branded drug and sold under there chemical name is known as generic drug. Generic drug marketed when a patent and exclusivity protection of research product is ended and when patent owner waives its rights or the requirement of FDA are met.

The FDA aspires to continually improve its pre- application interactions with applicants. To facilitate these interactions and to keep stakeholders as informed as possible, the agency provides the following resources and guidance on developing generic drug products and preparing and submitting abbreviated new drug applications (ANDAs).

**i. Product-Specific Guidance for Generic Drug Development**

To facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA regularly publishes product-specific guidance's describing the Agency's current thinking and expectations on how to develop therapeutic equivalents to specific reference listed drugs.

**ii. Generic Drug Approvals**

FDA regularly updates a listing of first generic drug approvals. To view all generic drug approvals and tentative approvals, use the "Drug Approval Reports by Month" feature on Drugs FDA and select "Original Abbreviated New Drug Approvals (ANDAs) by Month" for generic drug approvals or "Tentative Approvals by Month" for tentative approvals. The database is updated daily.

**iii. Pre-ANDA Program**

The Pre-ANDA Program is a valuable information resource for generic drug applicants. The program features product development assistance and pre-submission and mid-review cycle meetings to help clarify regulatory expectations early in product development and during application review.

**i. List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic**

The FDA maintains a list of approved new drug application (NDA) drug products that are no longer protected by patents or exclusivities, and for which the FDA has not approved an ANDA referencing that NDA drug product.

**ii. Authorized Generic Drugs**

The FDA List of Authorized Generic Drugs, updated quarterly, includes the drug trade name, the brand company manufacturer, and the date the authorized generic drug entered the market.

**iii. Quality by Design (QbD)**

QbD is a scientific, risk-based, proactive approach to pharmaceutical development, incorporating deliberate design effort and appreciating how processes impact product performance. FDA has published two QbD report examples:

**a. Inactive Ingredient Database**

The Inactive Ingredient Database provides information on inactive ingredients present in FDA-approved drug products, and can be used as an aid in developing generic drug products.

**b. Hatch-Waxman Letters**

The FDA has posted certain letters reflecting FDA's decisions on 180-day exclusivity and other matters related to generic drug approvals.

**iv. FDA Letters to Industry**

This series of letters informs generic drug product manufacturers of policy and procedure developments with respect to the Drug Price Competition and Patent Term Restoration Act of 1984.

**v. Bioequivalence Study Retention Samples**

The FDA provides requirements for retaining samples of drug products used in bio-availability and bioequivalence testing. Regulations state that applicants shall retain reserve samples of the tested products administered to study subjects and release these samples to FDA upon request.

## **Educational Resources**

The FDA Center for Drug Evaluation and Research Small Business & Industry Assistance program offers a variety of multimedia learning resources. The CDER SBIA Learn web page has many helpful courses and recordings in the "Generic Drugs" section.

## **Process of generic product development**

The process of generic product development first needs the physical development of any product which will require a formulator to:

Choose from the same types of available excipients.

Choose from the same types of available processes.

Utilize similar types of equipment, in similar types of facilities, meeting similar regulations.

Some people still truly believe that generic products are inferior to brand name products. However, the facts are:

Generic products must meet the same quality standards as brand name products. The efficacy of generic products vs. the designated reference product must be proven through the use of a bio-equivalency study. The facilities and procedures used to manufacture generic products must meet the same cGMP requirements as brand name products. Admittedly, there can be both good product development and poor product development practices in either brand name or generic pharmaceutical companies. Fortunately, stricter regulatory and process validation requirements have helped to weed out poorly

developed products making the proper development of robust formulations more essential than ever. Although this information primarily concerns solid oral dosage forms, many of the general principles discussed here would be applicable to generic semi-solid or liquid products as well.

### **Prior to Development**

A product for development must be selected. In order to properly select a product, input is needed from a variety of disciplines including:

- R&D
- Regulatory Affairs
- Legal
- Marketing & Sales
- Finance, etc.

Once selected, details of the selected product should be recorded into some kind of document to include information such as:

- Innovator Product Description and Dosage Form
- Innovator Product Packaging Description
- Innovator Product Sales
- Generic Product Description and Dosage Form
- Generic Product Packaging Description
- Generic Sales Forecasts
- Intended Manufacturing Site
- Intended Production Batch Size
- Any other relevant information

Based on patent expiry, product exclusivity, forecasts, availability of the active ingredient etc., the project needs to be scheduled and its' progress tracked and managed with the goal of being the first generic drug manufacturer (for that particular product) on the market.

### **Pre-formulation**

Prior to preparing actual trial formulations, "pre-formulation" work must be performed to obtain as much information about the reference product and drug substance as possible.

Common pre-formulation activities include the following:

Review of the product selection document

Review of any pertinent patent information

Obtain samples of reference product and packaging

Evaluate physical characteristics of the reference product

Determine reference drug release characteristics through "in-vitro" dissolution profiling.

Characterize drug substance to determine drug form (i.e. crystalline, powder, amorphous), drug solubility, polymorphism, particle size, bulk density, flow characteristics, chemistry (i.e. pKa, functional groups), drug absorption characteristics (pharmacokinetics), incompatibilities, sensitivities (light, heat, moisture), etc.

Identify a discriminating dissolution procedure with relevant in-vitro/in-vivo correlations.

Following these "pre-formulation" activities, decisions can be made as to the type of formulation and process to be considered for development. (Dosage form and dosage strength are determined by the reference product itself, and by the requirements detailed in the product selection document.)



There are three general processes used to produce tablets and capsules, as follows:

### **Direct Mix**

This process involves simply blending the drug substance with excipients and compressing the mixture into tablets or filling it into capsule shells.

### **Dry Granulation**

This process involves processing the drug substance with excipients using a “slugging” or “compaction” technique followed by “granulation sizing” and final blending with additional excipients prior to tablet compression, or capsule shell filling.

### **Wet Granulation**

This process involves processing the drug substance with excipients and a solvent in which a binder may be dissolved to produce a granulation. The granulation is subsequently dried, sized and blended with additional excipients prior to tablet compression or capsule shell filling.

Whenever possible or practical, a direct mixing process is initially considered since this process usually offers the simplest and most economical means to produce a solid pharmaceutical dosage form. However, the product dosage, physical drug characteristics, and even characteristics of the reference product itself, will ultimately determine what type of process is feasible.

A tablet or capsule dosage form will generally contain the following components:

**Active Ingredient-** Drug substance

**Binder-** Holds filler and drug particles together in agglomerates to form granules or tablets or capsule slugs, etc.

**Solvent-** Used in “wet granulations” as the granulating medium

**Fillers/Diluents-** Used to provide bulk or weight to tablets and capsules to make tablets or capsules of a practical size for administration

**Disintegrating Agent-** Used to cause granules and/or tablets and/or capsule contents to break apart to enhance the availability of drug substance for dissolution and absorption

**Glidant-** Used to reduce inter-particulate friction thereby improving flow characteristics

**Anti-adherent-** Similar role as lubricant, but more specialized for effectiveness at preventing adhesion to equipment surfaces. (Should be used in combination with a lubricant.)

**Lubricant-** Used to prevent sticking of powders to equipment used to compress tablets or fill capsule shells (i.e. tablet punches and dies, encapsulating dosators or tamping pins).

### **Others**

**Dyes-** Impart a colour to the tablet

**Sweetening Agents & Flavours-** Used in chewable tablets.

**Wetting Agents-** Used to enhance drug substance ‘wetting’ and solubility.

**Acidifying Agents, Buffers, Stabilizers, Etc.-** Excipients added to provide a more stable environment for the drug substance involved.

**Film Coating Preparations-** If a tablet is to be film-coated, the components of the material used for coating will include a polymeric film-former, a plasticizer, and may or may not include, an opacifying agent, a dispersing agent, one or more dyes, etc.

It is impossible to list every conceivable example or potential use for the large number of excipients available to fulfill the various roles as components of tablet and capsule formulations.

Therefore, only some of the most common excipients and their suggested use levels are listed as follows:

**Binders:**

Polyvinylpyrrolidone (PVP)-0.5-5%  
Pregelatinized starch - 5-10% (wet), 5-20% (direct)  
Starch paste- 5-25% w/w  
Microcrystalline cellulose - 5-25% (wet), 5-25% (direct)  
Sucrose- 50-70% solution  
Hydroxypropyl cellulose- 4-6%  
Ethylcellulose- 5% solution  
Methylcellulose- 1-5% solution (depending on viscosity grade)  
Acacia- 1-5%

**Solvents:**

Purified water  
Ethanol  
Purified water/ethanol  
Other organic solvents (i.e. Methylene Chloride)

**Fillers/Diluents:**

Microcrystalline cellulose  
Lactose  
Starch/pregelatinized starch  
Dicalcium phosphate  
Calcium carbonate  
Compressible sugars  
Mannitol  
Sorbitol

**Disintegrating Agents:**

Sodium starch glycolate- 4-8%  
Croscarmellose sodium- 3-6%  
Pregelatinized starch- 5-10%  
Starch- 5-10%  
Microcrystalline cellulose- 5-15%  
Cross-linked polyvinylpyrrolidone- 2-5%  
Alginic Acid- 5-10%

**Glidants/Lubricants/Antiadherents:**

Fumed silicon dioxide (glidant)-0.1-0.5% (anti-adherent)-1-2%  
Talc (anti-adherent)- 1-4%  
Magnesium stearate- 0.25-1.5%  
Stearic acid- 0.5-3%  
Hydrogenated vegetable oils- 2-5%  
Sodium lauryl sulfate- 1-3%  
Mineral oil- 1-3%

**Others:**

Dyes- Usually aluminum lakes: water soluble dyes precipitated with the hydrous oxide of aluminum.

Sweetening Agents & Flavours- Compressible sugars/alcohols & various flavouring agent

Wetting Agents- Sodium lauryl sulfate- 0.1-2%,

Polysorbate 80- 0.1-3%

Acidifying Agents, Buffers, Stabilizers, etc.-

Citric acid- 0.3-2%

Sodium citrate- 0.3-2%(dihydrate)

Sodium phosphate monobasic

**Considerations for Selecting Excipients in a Formulation**

Composition of Reference Product (if available)- PDR, CPS or product labels will often list qualitative composition of formulations.

**Requirement for Specific Excipient**

Formulations should start out simple, with additional, specialized excipients being incorporated as needed through experimental trials.

**Drug/Excipient Incompatibilities**

Drug characterization and pre-formulation studies may exclude specific excipients due to potential incompatibility or stability issues.

**Excipient Characteristics/Affect on Drug Substance Release**

Depending on the drug substance, certain excipients may be selected due to their affect at enhancing or retarding the release of the drug substance to produce the desired “in-vitro” dissolution release profile.

**Formulation Process**

Certain excipients are specialized for direct mixing processes whereas others are more suitable for wet granulation processes.

**Availability**

Excipients most readily available are usually selected over excipients that may be equally adequate, but not readily available.

**Experience**

Formulators usually select excipients with which they have the most experience, even though there may be equivalent excipients to perform the same function.

**Cost**

With two functionally equivalent, equally available excipients, the cheaper of the two may be selected.

**Formulation Development**

Once pre-formulation work and a development strategy are completed, a series of small-scale trials are prepared. These trials involve processing the drug substance with excipients using the selected process to produce a dosage form with the desired strength and appearance dictated in the product selection document. The dosage form is then physically and chemically evaluated to determine its acceptability relative to the reference product.

The following represents the common types of testing performed on tablet and capsule formulations under development:

### **Blends**

Physical Testing: Bulk and tapped density, particle size distribution, flow index, angle of repose, moisture and/or L.O.D.

Chemical Testing: Blend uniformity

### **Tablets**

Physical Testing: Appearance, average weight and weight variation, hardness, thickness, friability, disintegration time

Chemical Testing: Dissolution profiles vs. reference product, assay, content uniformity, chemical identification, impurities and related substances, ICH stability

### **Capsules**

**Physical Testing:** Appearance, average weight and weight variation, disintegration time

**Chemical Testing:** Dissolution profiles vs. reference product, assay, content uniformity, chemical identification, impurities and related substance, ICH Stability

Development trials continue until a formulation with a matching dissolution profile, relative to the reference product, is obtained in one or more dissolution media.

This formulation should then be scaled-up to a slightly larger size and the resulting dosage form packaged, and placed on accelerated stability stations for monitoring. In the meantime, additional trials should be prepared to optimize various formulation and process parameters.

These optimization trials are very important and serve to:

Provide experience with the new formulation and process.

Determine limitations by challenging various process parameters

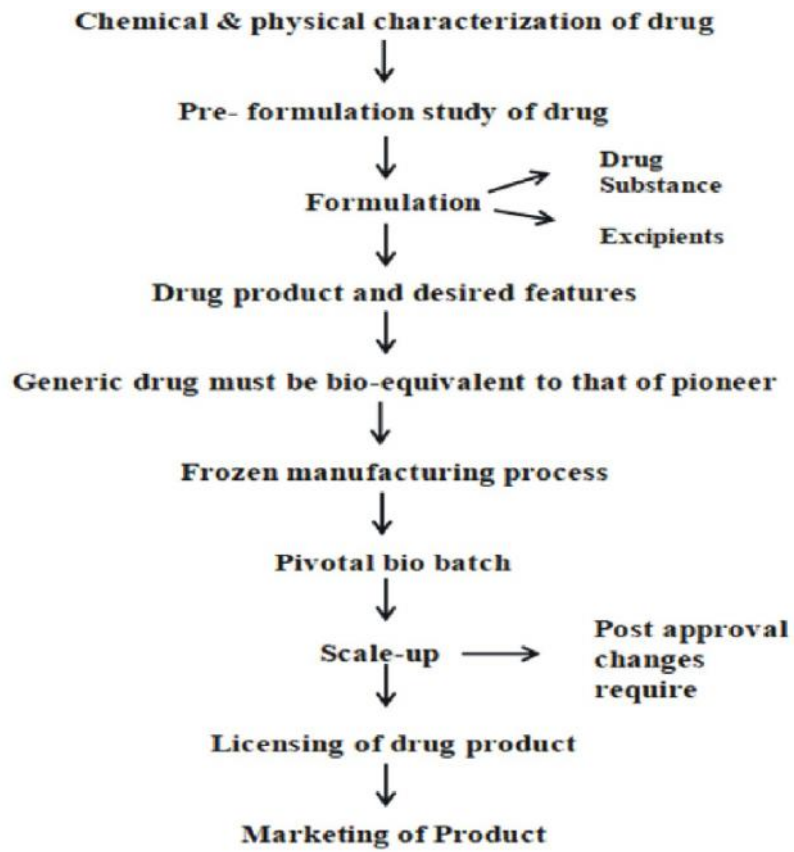
Provide additional data necessary for setting meaningful specifications

Identify significant formulation or processing issues that can be addressed *before* the product formulation and process is “locked” (i.e. prior to bioequivalency testing)

If the product retains acceptable physical and chemical characteristics, it is further scaled-up under GMP conditions to serve as the “test batch” for “in-vivo bioequivalency testing” vs. the reference product. If the product proves to be “non-bioequivalent” to the reference product, *reformulation is required*, assuming that the continued development of this product remains economically viable due to this delay.

If the product proves to be “bioequivalent” to the reference product, a submission package is assembled and submitted to the respective Government Regulatory Agency for review and eventual approval.

The key to a successfully developed generic product goes beyond a successful bioequivalency study, product approval, and a successful process validation study. A truly successful generic product is a product that can be made repeatedly, by any trained operator, on any qualified piece of equipment, at any time of the year, without any problems. The complete procedure for generic drug development is depicted in figure 7.



**Figure 7 :** Generic Drug Product Development

## **CHAPTER 01**



### **Regulatory Approval Process**

**Approval processes and time-lines involved in Investigational New Drug (IND)**

**New Drug Application (NDA)**

**Abbreviated New Drug Application (ANDA)**

**Changes to an approved NDA / ANDA**

## **CHAPTER 02**



### **Regulatory authorities and agencies**

**Overview of regulatory authorities of (Organization structure and types of applications):**

**India**

**United States**

**European Union**

**Australia**

**Japan**

**Canada**



## Background

A regulatory process, by which a person/ organization/ sponsor/ innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, application to marketing authorization of drug and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs.

## Investigational Product

ICH GCP defines an investigational product as,

“A pharmaceutical form of an active ingredient or place bobeingtested or used a sa reference in a clinical trial”(ICHGCP1.33).

This may include a marketed product that is being used in a different form than the one it was approved for, or a marketed product being used for an unapproved or new indication.

## Definition of an Investigational New Drug

The Code of Federal Regulations (CFR) defines an investigational new drug as: “A new drug or biological drug that is used in a clinical investigation.”

In the U.S. Food and Drug Administration (FDA) regulations, an investigational new drug is any substance (suchasadrug, vaccine or other biological product) for which FDA approval is being sought.

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## Investigational New Drug Application

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## Background

An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

An **investigational new drug** is a new drug or biological drug that is used in a clinical investigation. This term also includes biological products used in vitro for diagnostic purposes. The **Investigational New Drug Application (IND)** is a request for an exemption from the federal statute that prohibits an unapproved drug from being shipped in interstate commerce.

IND is **not** an application for marketing authorization of a drug. For the purpose of this lesson, “IND” is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.” Upon completion of preclinical study and collection of data, the **sponsor** (the person who takes responsibility for and initiates a clinical investigation) must submit an application to FDA to notify FDA it is conducting a clinical study on human subjects.

This application is called an Investigational New Drug Application (INDA or IND). Investigational new drug application abbreviated as INDA is a mandatory requirement filed with the FDA in order to seek permission for administering a new drug under investigation to Human subjects after completion of the preclinical studies on it.



	Preclinical Testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5	File IND at FDA	1	2	3	File NDA at FDA	2.5	12 Total	Additional Post marketing testing required by FDA
Test Population	Laboratory and animal studies		20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers		Review process/ Approval		
Purpose	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use				
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

It confers protection to the subjects and also sees that the investigational plan is efficient and designed to achieve its required objectives.

The sponsor of the drug is responsible for the initiation of clinical trials.

He might be an individual i.e. sponsor-investigator, a pharmaceutical company, governmental agency, academic institution or private or public organization.

The INDA is filed with the FDA under Title 21, Code of Federal Regulations Section 312- the guidelines for preapproval of all clinical testing's are specified.

### **Content of Investigational New Drug Application**

1. All the requirements for submitting an INDA are prescribed in the Code of Federal Regulations and are submitted under a cover sheet (Form FDA- 1571).
2. The items required are:
  - i. Name, address and telephone number of the sponsor of the drug.
  - ii. Name and title of the person responsible for monitoring the conduct and progress of the investigation.
  - iii. Names and titles of the persons responsible for the review and evaluation of information relevant to the safety of the drug.
  - iv. Name and address of any contract research organization involved in the study (if any).
  - v. Identification of the phase/phases of clinical investigation to be conducted.
  - vi. Introductory statement and general investigational plan including, name of drug and all active ingredients, structural formula and pharmacological class, formulation, route of administration, and broad objectives and planned duration of study.
  - vii. Description of the investigational plan.
3. The reason for selecting a drug or research study. Indications to be studied, approach to evaluation of the drug, types of studies, estimated number of subjects to be given the drug, and any risks anticipated based on animal studies.
  - i. Brief summary of previous experience with the drug, including reasons if the drug is withdrawn.

- ii. Chemistry and manufacturing control information like physical, chemical and biologic characteristics, product stability during the clinical investigation.
  - iii. Pharmacological and Toxicological information.
  - iv. If the drug is a combination of previously investigated components, then preclinical and clinical data of these components when given singly and in combination.
  - v. Clinical protocol for planned study.
  - vi. Commitment that an “Institutional Review Board” (IRB) has approved the study and will continue to monitor the investigation.
  - vii. Investigators brochure.
  - viii. Commitment not to begin clinical investigations until IND is in effect signature of the sponsor or authorized representative and the date of signed application.
4. After submission of IND to the FDA, it is assigned to the various divisions of Center for Drug Research and Evaluation wing of the FDA for its review and evaluation.
5. The FDA has 30days from the receipt of IND to decide whether the proposed clinical trial should proceed or not. If the sponsor is not contacted within 30days, the trial may proceed.
6. Meanwhile reviewers at FDA may put a “Clinical Hold” on the proposed Clinical trials at any time. This prevents human testing of drug. It may be due to the following reasons
- i. If there is any unreasoned threat to the safety of the trial subjects i.e. if the subjects face any illness or injury due to treatment.
  - ii. Insufficient data to assess patient risks.
  - iii. If the investigators involved in the study do not meet the necessary requirements with respect their qualification.
  - iv. Misleading or incomplete investigators brochure.
7. In case if all the requirements for FDA approval are satisfied an IND is granted. Once an IND is in effect, all the proposed changes to the original IND thereafter, must be submitted as amendments for approval.

## **Requirements of IND Application**

The FDA imposes substantial requirements and conditions on therapeutic drug products, including lengthy and detailed laboratory and clinical testing procedures, sampling activities, and other costly and time-consuming processes. After preclinical testing, as required by the applicable regulations, an Investigational New Drug (IND) application must be filed with the FDA to obtain authorization for human testing through clinical trials. This application includes a description of the overall plan for investigating the drug product and a comprehensive protocol for planned studies. Pursuant to the regulations, the FDA usually asks companies to submit a description of the drug substance, including its physical, chemical, and biological characteristics, as well as a description of the general method of preparation of the drug substance and a list of all components, including inactive ingredients. A section of the IND describes the composition, manufacture, and control of the drug substance. The drug company must provide sufficient information to assure the proper identification, quality, purity, and strength of the investigational drug. The IND should also contain adequate information about pharmacological and toxicological studies of the drug, involving laboratory animals and other tests on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical trials. Where there has been widespread use of the drug outside of the U.S., it is possible in some limited circumstances to submit a well-

documented clinical experience as part of the required preclinical work. Once the FDA approves the IND, the sponsor is allowed to enter the clinic where certain reporting requirements, such as making progress reports on the study or studies covered by the IND, must be met and the sponsor must alert the FDA and clinical investigators immediately of any unforeseen serious side effects or injuries.

## **Approval processes and time-lines involved in Investigational New Drug (IND)**

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

### **IND categories**

Commercial

Research (non-commercial)

**The IND application must contain information in three broad areas:**

#### **1. Animal Pharmacology and Toxicology Studies**

Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

## **2. Manufacturing Information**

Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

## **3. Clinical Protocols and Investigator Information**

Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the

## **4. Qualifications of clinical investigators**

professionals (generally physicians) who oversee the administration of the experimental compound to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

## **The labeling of an investigational new drug**

Must include the following statement: "Caution: New Drug-Limited by Federal (or United States) law to investigational use."

Must not be false or misleading and should not imply that the drug is safe or effective for the investigational purpose.

## **Control of an Investigational New Drug**

An investigational new drug may be given to participants only under supervision by the principal investigator or by a sub-investigator. (Usually, the person supervising the administration of an investigational new drug is a physician.) The investigator cannot supply the investigational new drug to any person who is not authorized to receive it.

Research that involves the use of controlled substances must comply with U.S. Drug Enforcement Administration regulations (21 CFR 1300-end). When studying an investigational new drug that is considered a controlled substance, the investigator must take adequate precautions to prevent theft or diversion of the drug into illegal channels of distribution. Such precautions include storing the investigational new drug "in a securely locked, substantially constructed cabinet or other securely locked, substantially constructed enclosure, access to which is limited." Promotion of and Charging for Investigational New Drugs.

Neither an investigator nor a sponsor may promote (that is, endorse or advertise) an investigational new drug as safe or effective for the investigational purpose. In addition: An investigational new drug cannot be distributed commercially or in a test market.

An investigation cannot be prolonged "after finding that the results of the investigation appear to establish sufficient data to support a marketing application." In other words, if there is good evidence that the investigational new drug is safe and effective, the study should be stopped and no other participants enrolled.

Charging for an investigational new drug in a clinical trial is not permitted without approval from the FDA unless the drug is being provided for treatments.

## **Phases of Clinical Trials of Investigational New Drugs**

Clinical trials of an investigational new drug are generally conducted in four phases, Phase 1 to Phase 4. Phase 0, or “exploratory” trials, also exist as small clinical trials (sometimes only a few participants) that involve dosing at a sub-therapeutic level. Phase 0 trials are not as prevalent as Phases 1-4. Each phase is designed to find out different information. Although the phases of a trial are usually conducted sequentially (one after another), they sometimes overlap.

Individuals may be eligible for studies in different phases, depending on their age, general condition, the type and stage of their disease, and previous therapy, if any.

### **1. Phase 1 Trials**

Phase 1 trials are the first studies of an investigational new drug in humans. They are usually conducted in healthy volunteers. In some cases, Phase 1 trials may be conducted in individuals who have the disease the drug is intended to treat. Phase I trials generally involve between 20 and 80 participants.

Phase 1 trials are designed:

Make a preliminary determination of the drug’s safety in humans. Identify some of the side effects associated with the drug’s use.

Begin to define a safe therapeutic (healing) dose range.

### **2. Phase 2 Trials**

Phase 2 trials are usually conducted in individuals who have the disease the drug is intended to treat or are at high risk for developing the disease. Phase 2 trials are larger than Phase 1 trials but still relatively small, usually involving no more than several hundred participants.

Phase 2 trials are designed to:

Begin to evaluate the drug’s effectiveness in treating or preventing the disease or condition of interest.

Determine the optimal dosing of the drug.

Determine the common short-term side effects and risks associated with the drug.

### **3. Phase 3 Trials**

Phase 3 trials are conducted after preliminary evidence from Phase 1 and 2 trials suggests that the investigational new drug is safe and effective. They usually include between several hundred and several thousand participants.

Phase 3 trials are designed to:

Gather additional information about the drug’s safety and effectiveness to evaluate whether its benefits outweigh its risks.

Compare it to other commonly used treatments for the same condition (if available) or compared to a placebo. These studies can be performed in a blinded manner.

Evaluate interactions with other treatments that may be used at the same time as the investigational new drug.

Provide adequate information to determine the indication for which the drug will be labeled fit is approved for marketing as well as any limitations on the drug’s use that should be stated in the labeling. For example, if there were insufficient information to show that a drug can safely be given to children, the labeling would restrict the drug’s use to adults.

## **4. Phase 4 Trials**

Phase 4 trials are conducted after the drug or treatment has been approved for marketing. They are designed to:

Continue testing the drug or treatment to collect additional short-term safety information.

Collect information about the effect of the drug or treatment in various populations. Collect information about side effects associated with long-term use of the drug

### **IND Protocol Amendments**

The sponsor of an IND must submit a protocol amendment to the FDA: To describe any change in a Phase 1 protocol that significantly affects the safety of participants; or to describe any change in a Phase 2 or Phase 3 protocol that significantly affects the safety of participants, the scope of the investigation, or the scientific quality of the study.

### **IND Safety Reports**

Sponsors must promptly review and investigate all information they receive relevant to the safety of an investigational new drug that is received from any source, foreign or domestic, including information derived from: Clinical or epidemiological studies, Animal studies, Commercial marketing experience, Reports in the scientific literature, unpublished scientific papers, and Reports from foreign regulatory authorities. The sponsor must notify the FDA of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but not later than 7 calendar days after the sponsor's initial receipt of the information. Sponsors must provide written notification to the FDA and to all investigators participating in a trial within 15 calendar days of any adverse event that is:

Both serious, unexpected and reasonably likely to have been caused by the investigational new drug. Subsequent, appropriate follow-up information must also be submitted, a site becomes available. The sponsor must also provide written notification of any finding from tests in laboratory animals that suggests a significant risk for human participants. The written notification must be provided as soon as possible and no later than 15 calendar days after the sponsor receives the information.

### **IND Information Amendments and Annual Reports**

A sponsor must file an information amendment to report essential information about the IND that is not within the scope of a protocol amendment, IND safety report, or annual report. The following are examples of information that requires the filing of an information amendment:

New information about technical features of the drug, such as its toxicology or chemistry.

Discontinuation of a clinical investigation.

Within 60 days of the first anniversary of the date the IND went into effect, and every subsequent year, a sponsor must submit a brief report of the progress of the investigation. This annual report must include: A brief summary of the status of each study in progress or completed. A summary of the most frequent and most serious adverse experiences. A summary of all IND safety reports submitted. A list of participants who died during participation in the investigation, with the cause of death for each participant. A list of participants who dropped out as a result of any adverse experience, whether or not the adverse experience is thought to be related to the investigational new drug. A summary of the general investigational plan for the upcoming year. An updated Investigator's Brochure, if available. A summary of any foreign market developments. A summary of any outstanding business with the FDA regarding the IND (i.e. a response to an FDA request for information)



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# Investigational New Drugs Responsibilities

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## 1. Responsibilities of Sponsors

Both sponsor and investigators who are involved in conducting a clinical trial under an IND filed with the FDA must accept and fulfill certain responsibilities.

Sponsors' responsibilities include: Selecting qualified investigators, providing investigators with the information they need to conduct the investigation, ensuring proper monitoring of the trial, Ensuring the trial is conducted according to the plan and protocols contained in the IND, Informing the FDA and all investigators of significant new adverse effects or risks that are reasonably likely to be caused by the investigational new drug. Maintaining proper records, disposing of unused supplies of the investigational new drug. Unless the sponsor is a sponsor-investigator, the sponsor does not actually conduct the investigation. Based on GCP guidelines, other Sponsor responsibilities include (ICH GCP E6, 5.12; 5.13; 5.14): Ensuring that the Investigational Product is manufactured in accordance with Good Manufacturing Practices. Ensuring that Investigational Product is packaged in a way that prevents contamination and unacceptable deterioration during transport and storage. Supplying investigators/institutions with the Investigational Product. Having written procedures that include instructions on the handling and storage of Investigational product that sites should follow. Maintaining sufficient quantities of the Investigational Product used in the trial to reconfirm specifications should he need arise. The above represent good examples of responsibilities the Sponsor may transfer to a Contract Research Organization (CRO), such as a clinical coordinating center. However, the ultimate responsibility for Investigational Product resides with the Sponsor. Any Investigational Product-related duties and functions that are transferred to and assumed by a CRO are specified in writing.

## 2. Responsibilities of Investigators

Investigators' responsibilities include:

Providing the sponsor with a completed, signed Statement of Investigator. (Form FDA 1572. Conducting the trial in accordance with the signed investigator statement, protocol, and applicable regulations. Protecting the rights, safety, and welfare of trial participants. Obtaining informed consent from all trial participants. Maintaining proper records. Furnishing all required progress reports, safety reports, financial disclosure reports, and a final report. Complying with Institutional Review Board review and Ensuring the proper handling of controlled substances. This topic is also discussed in the Roles and Responsibilities module. Based on GCP guidelines, other Investigator responsibilities include (ICH GCP E6, 4.6): Ensuring Investigational Product Accountability Assigning duties for Investigational Products to a pharmacist or an appropriate individual who has the necessary license for dispensing. Maintaining records of the Investigational Product from delivery at the site to dispensing to the participant as well as use by the participant, return by the participant, and reconciling all product prior to destruction. Ensuring that the Investigational Product is used in accordance with the approved protocol. Explaining the correct use of the Investigational Product to each participant and checking at intervals that each participant is following instructions properly.

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## New Drug Application (NDA)

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### Background

For decades, the regulation and control of new drugs in the United States has been based on

the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United State. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality and purity.

NDA is an application submitted to the FDA for permission to market a new drug. To obtain this permission a sponsor submits preclinical and clinical test data to NDA for analyzing the drug information, description of manufacturing procedures.

After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application that is FDA formal review. At the conclusion of FDA review of an NDA, there are 3 possible actions that can send to sponsor: Not approvable- in this letter list of deficiencies and explain the reason. Approvable - it means that the drug can be approved but minor deficiencies that can be corrected like-labeling changes and possible request commitment to do post-approval studies. Approval- it states that the drug is approved. If the action taken is either an approvable or a not approvable, then FDA provides applicant with an opportunity to meet with agency and discuss the deficiencies.

## **New Drug Application**

A new drug application (NDA) is a comprehensive document that must be submitted to the U.S. Food and Drug Administration (FDA) in order to request approval for marketing a new drug in the United States.

## **NDA Classifications**

NDA Classifications CDER classifies new drug applications with a code that reflects both the type of drug being submitted and its intended uses.

- New Molecular Entity
- New Salt of Previously Approved Drug
- New Formulation of Previously Approved Drug
- New Combination of Two or More Drugs
- Already Marketed Drug Product – Duplication by new manufacturer
- New Indication for Already Marketed Drug, including switch in status to OTC (conversion of prescription drug to OTC)
- Already Marketed Drug Product without previously Approved NDA

## **NDA Requirements**

- Content and format of application



- Formatting, assembling and submitting new drug and antibiotic applications
- NDA summary format and content
- NDA technical sections
- Abbreviated new drug application

## **1. Content and format of application**

Although the exact requirements are a function of the nature of a specific drug, the NDA must provide all relevant data and information that a sponsor has collected during the product's research and development.

## **2. Formatting, assembling and submitting new drug and antibiotic applications**

### **A. Application format**

The NDA regulations require the submission of Archival copy and Review copy.

#### **i. Archival copy :**

This is a complete copy of an application submission and is intended to serve as a reference source for FDA reviewers. This contains information which not contained in the review copy.

#### **ii. Review copy :**

It is divided into five (or six) sections containing technical and scientific information required by FDA reviewers. Each of sections of review copy is separately bound. It should be provided with following: A copy of cover letter. A copy of application form (FDA 356h) A copy of overall summary A copy of index to the entire application An index to the specific review section Both copies are submitted in hard copy.

### **B. Assembling the application**

#### **Folders**

Because of the procedure used at the FDA to file and retrieve material from the document rooms where applications are kept, it is necessary that applicants use the colored folders to bind the archival copy and each technical section. The cover of each folder should bear the NDA number (if known), name of applicant and name of drug product.

#### **Paper size and binding**

All applications must be bound on the left side of the page using the United States standard size loose leaf page. (8.5" x11" ).

#### **Pagination**

All pages in the application must be numbered and numbering of review copy pages should be same as the numbering of corresponding pages in archival copy.

#### **Volume size and identification**

Volume submitted in hard copy form should be no more than 2 inches thick.

#### **Packing carton**

The box size of 14" \*12" \*9.5" is recommended for shipment of applications to FDA. Because ANDAs are handled and stored separately, smaller boxes may be appropriate for them.

## **Supplements, Amendments and Post marketing Reports**

The submission format for amendments to pending applications and supplements to approved applications will be same as an original application. Each submission will consist of two copies: a complete archival copy and an appropriately segmented review copy. Amendments, supplements, resubmissions annual reports and other correspondence concerning full applications should be addressed to appropriate FDA reviewing divisions.

### **C. Application content**

#### **Full application**

##### **Archival copy**

The archival copy should confirm the agreement between the FDA and the applicant. The letter should cite any relevant meetings by date and topic, and identify one or more persons the FDA may contact regarding the application. The letter may include any other information the applicant wishes to convey to the FDA about the application. The archival copy is required to contain the following: Application form (FDA 356h) it serves as a cover sheet for the application, contains basic identifying information about the applicant and the drug product. The application form, as well as the index and the summary should be bound together in a single volume. Patent information on the applicant's drug and a patent certification with respect to the drug should be submitted on a separate piece of paper attached to the application form itself.

### **3. NDA Summary Format and Content**

Summary should provide sufficient detail. Data should be provided in tabular or graphical form,. Summary should be between 50-200 pages.

#### **Annotated package insert**

This section include proposed text of the labeling for the product. The proposed text of the package labeling must be annotated by reference to volume and page number to the information in the summary and in technical sections of the applications.

#### **Pharmacological class, scientific rationale, intended use and potential clinical benefits**

A brief statement should be included to identify the pharmacological class of the drug, the scientific rationale for the drug, its intended use, and its potential clinical benefits.

#### **Chemistry, Manufacturing and Controls**

This summary must provide overview of the drug substances and the drug product.

- 1. Drug substance:** It includes description about of drug substance, physical and chemical characteristics and stability of the drug substance.
- 2. Drug product:** It includes information about:
  - a. Composition and dosage form
  - b. Name and address of manufacturer
  - c. Container and closure system
  - d. Stability
  - e. Specifications for drug product and test methods to assure the specifications

## **Foreign Marketing History**

If the product is marketed outside the U.S., regardless of the dosage form, strength, salt, ester, or complex of the drug, the marketing history should be provided. This should include a list of countries in which drug product is marketed, with dates of marketing, if known. It must also include a list of any countries in which the drug has been withdrawn for any reason relating to safety or efficacy. Specific reason for withdrawal should be given.

## **Non- clinical Pharmacology and Toxicology Summary:**

It includes information about:

3. Pharmacology studies
4. Acute toxicity studies
5. Multi dose toxicity studies
6. Carcinogenicity studies
7. Special toxicity studies
8. Reproduction studies
9. Mutagenicity studies
10. ADME studies

## **Human Pharmacokinetics and bio-availability Summary**

It includes brief description about bio-availability study of drug, pharmacokinetic characteristic of active ingredient and dissolution profile of drug.

## **Microbiology Summary**

It provides summary of results of the microbiologic studies conducted with anti-infective and antiviral drug. This includes mechanism of action, antimicrobial spectrum of action and mechanism of resistance to the drug.

## **Clinical Data Summary and Results of Statistical Analysis**

It is the basis of efficacy and safety that will determine an NDA approval. The Clinical Data Summary and Results of Statistical Analysis are divided into several parts as described below: Clinical pharmacology Overview of Clinical Studies Controlled Clinical Studies Uncontrolled Clinical Studies Other studies and Information Safety summary (general Safety Conclusions).

### **4. NDA technical sections**

This includes brief description of the following sections.

## **Chemistry, Manufacturing and Controls**

It is the most critical portion of NDA or ANDA. This section must fully describe the composition of the drug substance (active ingredient), and its synthesis (or isolation) and purification, as well as applicable process controls, specifications, and analytical test methods.

## **Nonclinical Pharmacology and Toxicology**

It provides a description or summary of all animal and invitro studies with the drug.

1. Pharmacology Studies.
2. Acute Toxicity Studies.
3. Sub chronic/Chronic/Carcinogenicity Studies.

4. Special Toxicity Studies.
5. Reproduction Studies.
6. Mutagenicity Studies.
7. ADME Studies.

### **Human Pharmacokinetics and bio-availability Section**

For a new chemical entity (NCE), it is desirable to determine its bio-availability and pharmacokinetics from the dosage form, except that for certain dosage forms (e.g., iv solutions) 100% bio-availability may be assumed. For solid oral dosage forms (e.g., capsule or tablet) a bioequivalence study is often necessary to demonstrate that formulation proposed for marketing is bioequivalent to whatever formulations may have been employed in early clinical trial. The summary should include a table with following pharmacokinetic parameter: C<sub>max</sub>, AUC, T<sub>max</sub>, k<sub>el</sub>, V<sub>d</sub>, plasma and renal clearance and urine excretion.

### **Microbiology**

This section is of major importance for anti-infective drugs and includes data on the biochemical basis of the drug's action and its antimicrobial spectra; any known mechanisms of resistance to the drug; and clinical laboratory methods.

### **Clinical Data Section**

It is the most important and most complicated section of an NDA. It is the part that provides the safety and efficacy data on the drug for its intended use.

### **Outline of Clinical Section**

It includes

1. List of investigators; List of INDs and NDAs
2. Background / Overview of clinical investigations
3. Clinical pharmacology
4. Controlled clinical studies
5. Uncontrolled clinical studies
6. Other studies and information
7. Integrated summary of efficacy
8. Integrated summary of safety
9. Drug abuse and over dosage information
10. Integrated summary of benefits and risk of drugs

### **Samples, Methods Validation and Labeling**

Samples should not be submitted to the FDA with the application. The reviewing chemist will contact the applicant and provide the laboratory address where samples should be sent. The applicant should prepare four representative samples in sufficient quantity to permit FDA to perform each test described in the application three times to determine whether the drug substance and drug product meet the specification given in the application. The archival copy of an application is required to contain copies of the label and all labeling proposed for the drug product. Methods validation data must be provided in triplicate because copies are forwarded to two FDA laboratories.

## Case Report Forms and Tabulations

The sponsor must submit data tabulations from each Phase II and Phase III study and also the case study report form for every clinical trial patient who died or withdrew from the study because of an adverse event.

## Patent Information

Information must be submitted regarding any patent held by the sponsor that covers the drug substance, formulation, and composition of the drug product, or method of use. Upon approval of the NDA, this information is published in the FDA's Orange Book (known formally as Approved Drug Products with Therapeutic Equivalence Evaluations) and serves as a guide to firms wishing to develop generic copies of the innovator's product.

## 5. Abbreviated new drug application

An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references.

### Content and format of an NDA.

NDAs and supplements to approved NDAs are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the NDA are required: An archival copy, a review copy, and a field copy. An NDA for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other NDAs will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an NDA of the type described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, an amendment, and a supplement. The NDA is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of NDAs to assist applicants in their preparation.

**(a) Application form.** The applicant must submit a completed and signed application form that contains the following:

- (1) The name and address of the applicant; the date of the NDA; the NDA number if previously issued (for example, if the NDA is a resubmission or an amendment or supplement); the name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all INDs (as defined in § 312.3(b) of this chapter) that are referenced in the NDA; the identification numbers of all drug master files and other applications under this part that are referenced in the NDA; and the drug product's proposed indications for use.
- (2) A statement whether the submission is an original submission, a 505(b)(2) application, a resubmission, or a supplement to an application under § 314.70.
- (3) A statement whether the applicant proposes to market the drug product as a prescription or an over-the-counter product.
- (4) A check-list identifying what enclosures required under this section the applicant is submitting.

- (5) The applicant, or the applicant's attorney, agent, or other authorized official must sign the NDA. If the person signing the NDA does not reside or have a place of business within the United States, the NDA is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

**(b) Index.** The archival copy of the NDA is required to contain a comprehensive index by volume number and page number to the summary under paragraph (c) of this section, the technical sections under paragraph (d) of this section, and the supporting information under paragraph (f) of this section.

**(c) Summary.**

- (1) An NDA is required to contain a summary of the NDA in enough detail that the reader may gain a good general understanding of the data and information in the NDA, including an understanding of the quantitative aspects of the data. The summary is not required for supplements under § 314.70. Resubmissions of an NDA should contain an updated summary, as appropriate. The summary should discuss all aspects of the NDA, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel reviewing the summary in the context of their review of the NDA, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the NDA. To the extent possible, data in the summary should be presented in tabular and graphic forms. FDA has prepared a guideline under § 10.90(b) that provides information about how to prepare a summary. The summary required under this paragraph may be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under § 314.430(e)(2)(ii)) when the NDA is approved.
- (2) The summary is required to contain the following information:
  - (i) The proposed text of the labeling, including, if applicable, any Medication Guide required under part 208 of this chapter, for the drug, with annotations to the information in the summary and technical sections of the NDA that support the inclusion of each statement in the labeling, and, if the NDA is for a prescription drug, statements describing the reasons for omitting a section or subsection of the labeling format in § 201.57 of this chapter.
  - (ii) A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, its intended use, and the potential clinical benefits of the drug product.
  - (iii) A brief description of the marketing history, if any, of the drug outside the United States, including a list of the countries in which the drug has been marketed, a list of any countries in which the drug has been withdrawn from marketing for any reason related to safety or effectiveness, and a list of countries in which applications for marketing are pending. The description is required to describe both marketing by the applicant and, if known, the marketing history of other persons.
  - (iv) A summary of the chemistry, manufacturing, and controls section of the NDA.
  - (v) A summary of the nonclinical pharmacology and toxicology section of the NDA.



(vi) A summary of the human pharmacokinetics and bioavailability section of the NDA.

(vii) A summary of the microbiology section of the NDA (for anti-infective drugs only).

(viii) A summary of the clinical data section of the NDA, including the results of statistical analyses of the clinical trials.

(ix) A concluding discussion that presents the benefit and risk considerations related to the drug, including a discussion of any proposed additional studies or surveillance the applicant intends to conduct postmarketing.

(d) **Technical sections.** The NDA is required to contain the technical sections described below. Each technical section is required to contain data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the NDA or whether grounds exist under section 505(d) of the Federal Food, Drug, and Cosmetic Act to refuse to approve the NDA. The required technical sections are as follows:

(1) **Chemistry, manufacturing, and controls section.** A section describing the composition, manufacture, and specification of the drug substance and the drug product, including the following:

(i) **Drug substance.** A full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, tests, analytical procedures, and acceptance criteria relating to stability, sterility, particle size, and crystalline form. The NDA may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii) (a) **Drug product.** A list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product; the specifications for each component; the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems; and stability data with proposed expiration dating. The NDA may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, and analytical procedures. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(b) Unless provided by paragraph (d)(1)(ii)(a) of this section, for each batch of the drug product used to conduct a bioavailability or bioequivalence study described in § 320.38 or § 320.63 of this chapter or used to conduct a primary stability study: The

batch production record; the specification for each component and for the drug product; the names and addresses of the sources of the active and non-compendial inactive components and of the container and closure system for the drug product; the name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility; and the results of any test performed on the components used in the manufacture of the drug product as required by § 211.84(d) of this chapter and on the drug product as required by § 211.165 of this chapter.

(c) The proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product.

(iii) **Environmental impact.** The NDA is required to contain either a claim for categorical exclusion under § 25.30 or 25.31 of this chapter or an environmental assessment under § 25.40 of this chapter.

(iv) The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the NDA. FDA will review such early submissions as resources permit.

(v) The applicant must include a statement certifying that the field copy of the NDA has been provided to the applicant's home FDA district office.

(2) **Nonclinical pharmacology and toxicology section.** A section describing, with the aid of graphs and tables, animal and in vitro studies with drug, including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

(iii) Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

(v) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58 a statement that it was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(3) **Human pharmacokinetics and bio-availability section.** A section describing the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the submission of in vivo bioavailability data under subpart B of part 320, including the following:

(i) A description of each of the bioavailability and pharmacokinetic studies of the drug in humans performed by or on behalf of the applicant that includes a description of the analytical procedures and statistical methods used in each study and a statement with respect to each



study that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(ii) If the NDA describes in the chemistry, manufacturing, and controls section tests, analytical procedures and acceptance criteria needed to assure the bioavailability of the drug product or drug substance, or both, a statement in this section of the rationale for establishing the tests, analytical procedures, and acceptance criteria, including data and information supporting the rationale.

(iii) A summarizing discussion and analysis of the pharmacokinetics and metabolism of the active ingredients and the bioavailability or bioequivalence, or both, of the drug product.

**(4) Microbiology section.** If the drug is an anti-infective drug, a section describing the microbiology data, including the following:

(i) A description of the biochemical basis of the drug's action on microbial physiology.

(ii) A description of the antimicrobial spectra of the drug, including results of in vitro preclinical studies to demonstrate concentrations of the drug required for effective use.

(iii) A description of any known mechanisms of resistance to the drug, including results of any known epidemiologic studies to demonstrate prevalence of resistance factors.

(iv) A description of clinical microbiology laboratory procedures (for example, in vitro sensitivity discs) needed for effective use of the drug.

**(5) Clinical data section.** A section describing the clinical investigations of the drug, including the following:

(i) A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.

(ii) A description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study. If the study report is an interim analysis, this is to be noted and a projected completion date provided. Controlled clinical studies that have not been analyzed in detail for any reason (e.g., because they have been discontinued or are incomplete) are to be included in this section, including a copy of the protocol and a brief description of the results and status of the study.

(iii) A description of each uncontrolled clinical study, a summary of the results, and a brief statement explaining why the study is classified as uncontrolled.

(iv) A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the NDA, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data must be presented by gender, age, and racial subgroups and must identify any modifications of dose or dose interval needed for specific subgroups.

Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also must be presented.

(vi) A summary and updates of safety information, as follows:

(a) The applicant must submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data must be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also must be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(b) The applicant must, under section 505(i) of the Federal Food, Drug, and Cosmetic Act, update periodically its pending NDA with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These “safety update reports” must include the same kinds of information (from clinical studies, animal studies, and other sources) and must be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section. In addition, the reports must include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event (unless this requirement is waived). The applicant must submit these reports (1) 4 months after the initial submission; (2) in a resubmission following receipt of a complete response letter; and (3) at other times as requested by FDA. Before submitting the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

(vii) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdose is also required, including information on dialysis, antidotes, or other treatments, if known.

(viii) An integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling.

(ix) A statement with respect to each clinical study involving human subjects that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50.

(x) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer - in lieu of a listing of the specific obligations transferred - may be submitted.

(xi) If original subject records were audited or reviewed by the sponsor in the course of

monitoring any clinical study to verify the accuracy of the case reports submitted to the sponsor, a list identifying each clinical study so audited or reviewed.

**(6) Statistical section.** A section describing the statistical evaluation of clinical data, including the following:

(i) A copy of the information submitted under paragraph (d)(5)(ii) of this section concerning the description and analysis of each controlled clinical study, and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies.

(ii) A copy of the information submitted under paragraph (d)(5)(vi)(a) of this section concerning a summary of information about the safety of the drug product, and the documentation and supporting statistical analyses used in evaluating the safety information.

**(7) Pediatric use section.** A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under § 314.55.

**(e) Samples and labeling**

**(1)** Upon request from FDA, the applicant must submit the samples described below to the places identified in the Agency's request. FDA generally will ask applicants to submit samples directly to two or more Agency laboratories that will perform all necessary tests on the samples and validate the applicant's analytical procedures.

(i) Four representative samples of the following, each sample in sufficient quantity to permit FDA to perform three times each test described in the NDA to determine whether the drug substance and the drug product meet the specifications given in the NDA:

(a) The drug product proposed for marketing;

(b) The drug substance used in the drug product from which the samples of the drug product were taken; and

(c) Reference standards and blanks (except that reference standards recognized in an official compendium need not be submitted).

(ii) Samples of the finished market package, if requested by FDA.

**(2)** The applicant must submit the following in the archival copy of the NDA:

(i) Three copies of the analytical procedures and related descriptive information contained in the chemistry, manufacturing, and controls section under paragraph (d)(1) of this section for the drug substance and the drug product that are necessary for FDA's laboratories to perform all necessary tests on the samples and to validate the applicant's analytical procedures. The related descriptive information includes a description of each sample; the proposed regulatory specifications for the drug; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision and ruggedness; and complete results of the applicant's tests on each sample.

(ii) Copies of the label and all labeling for the drug product (including, if applicable, any Medication Guide required under part 208 of this chapter) for the drug product (4 copies of

draft labeling or 12 copies of final printed labeling).

- (f) **Case report forms and tabulations.** The archival copy of the NDA is required to contain the following case report tabulations and case report forms:
- (1) **Case report tabulations.** The NDA is required to contain tabulations of the data from each adequate and well-controlled study under § 314.126 (Phase 2 and Phase 3 studies as described in §§ 312.21 (b) and (c) of this chapter), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in § 312.21(a) of this chapter), and tabulations of the safety data from other clinical studies. Routine submission of other patient data from uncontrolled studies is not required. The tabulations are required to include the data on each patient in each study, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the NDA. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the NDA, in accordance with paragraph (f)(3) of this section.
  - (2) **Case report forms.** The NDA is required to contain copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo. This requirement may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study.
  - (3) **Additional data.** The applicant must submit to FDA additional case report forms and tabulations needed to conduct a proper review of the NDA, as requested by the director of the FDA division responsible for reviewing the NDA. The applicant's failure to submit information requested by FDA within 30 days after receipt of the request may result in the agency viewing any eventual submission as a major amendment under § 314.60 and extending the review period as necessary. If desired by the applicant, the FDA division director will verify in writing any request for additional data that was made orally.
  - (4) **Presentation and format.** Applicants are invited to meet with FDA before submitting an NDA to discuss the presentation and format of supporting information. If the applicant and FDA agree, the applicant may submit tabulations of patient data and case report forms in an alternate form.
- (g) **Other.** The following general requirements apply to the submission of information within the summary under paragraph (c) of this section and within the technical sections under paragraph (d) of this section.
- (1) The applicant ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found. A reference to information submitted to the agency by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.
  - (2) The applicant must submit an accurate and complete English translation of each part of the NDA that is not in English. The applicant must submit a copy of each original literature publication for which an English translation is submitted.

(3) If an applicant who submits an NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act obtains a “right of reference or use,” as defined under § 314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, the applicant must include in its NDA a written statement signed by the owner of the data from each such investigation that the applicant may rely on in support of the approval of its NDA, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its NDA.

(h) **Patent information.** The NDA is required to contain the patent information described under § 314.53.

(i) **Patent certification -**

(I) **Contents.** A 505(b)(2) application is required to contain the following:

(i) **Patents claiming drug substance, drug product, or method of use.**

(A) An appropriate patent certification or statement with respect to each patent issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims the drug substance or drug product on which investigations that are relied upon by the applicant for approval of its 505(b)(2) application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53. For each such patent, the applicant must provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant must entitle such a certification “Paragraph I Certification”;

(2) That the patent has expired. The applicant must entitle such a certification “Paragraph II Certification”;

(3) The date on which the patent will expire. The applicant must entitle such a certification “Paragraph III Certification”; or

(4) (i) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application is submitted. The applicant must entitle such a certification “Paragraph IV Certification”. This certification must be submitted in the following form:

I, (name of applicant), certify that Patent No. \_\_\_\_ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this 505(b)(2) application is submitted.

(ii) The certification must be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder (or, if the NDA holder does not reside or maintain a place of business within the United States, its attorney, agent, or other authorized official) for the drug product that is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(b) with respect to sending the notice and under § 314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act, an appropriate patent



certification or statement under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(C) If, before the date of submission of an original 505(b)(2) application, there is a drug product approved in an NDA that is pharmaceutically equivalent to the drug product for which the original 505(b)(2) application is submitted, an appropriate patent certification or statement under this section with respect to each patent that claims the drug substance or drug product or that claims an approved use for one such drug product.

(iii) **No relevant patents.** If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied upon in this 505(b)(2) application were conducted or that claim a use of such drug or drugs.

(iv) **Method-of-use patent.**

(A) If information that is submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 is for a method-of-use patent, and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent, a statement explaining that the method-of-use patent does not claim a proposed indication or other condition of use.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, the applicant must submit an applicable certification under paragraph (i)(1)(i) of this section.

(2) [Reserved]

(3) **Licensing agreements.** If a 505(b)(2) application is submitted for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant must submit a paragraph IV certification as to that patent and a statement that the applicant has been granted a patent license. If the patent owner consents to approval of the 505(b)(2) application (if otherwise eligible for approval) as of a specific date, the 505(b)(2) application must contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to approval of the 505(b)(2) application as of a specific date.

(4) **Untimely filing of patent information.**

(i) If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved NDA for the patented drug does not file with FDA the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification or statement is not required to submit a patent certification or statement to address the patent or patent information that is late-listed with respect to the pending 505(b)(2) application. Except as provided in § 314.53(f)(1),

an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information unless:

- (A) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of patent issuance;
  - (B) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of approval of a corresponding change to product labeling; or
  - (C) The amendment to the description of the approved method(s) of use claimed by the patent is submitted within 30 days of a decision by the U.S. Patent and Trademark Office or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent, and the amendment contains a copy of the decision.
- (ii) An applicant whose 505(b)(2) application is submitted after the NDA holder's untimely filing of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification or statement at the time of the patent submission must submit a certification under paragraph (i)(1)(i) of this section and/or a statement under paragraph (i)(1)(iii) of this section as to that patent.

#### **(5) Disputed patent information.**

If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn, the applicant must submit an appropriate certification or statement for each listed patent.

#### **(6) Amended certifications.**

A patent certification or statement submitted under paragraphs (i)(1)(i) through (iii) of this section may be amended at any time before the approval of the 505(b)(2) application. An applicant must submit an amended certification as an amendment to a pending 505(b)(2) application. If an applicant with a pending 505(b)(2) application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment is submitted to change the certification, the 505(b)(2) application will no longer be considered to contain the prior certification.

- (i) **After finding of infringement.** An applicant who has submitted a paragraph IV certification and is sued for patent infringement must submit an amendment to change its certification if a court enters a final decision from which no appeal has been or can be taken, or signs and enters a settlement order or consent decree in the action that includes a finding that the patent is infringed, unless the final decision, settlement order, or consent decree also finds the patent to be invalid. In its amendment, the applicant must certify under paragraph (i)(1)(i)(A)(3) of this section that the patent will expire on a specific date or, with respect to a patent claiming a method of use, the applicant may instead provide a statement under paragraph (i)(1)(iii) of this section if the applicant amends its 505(b)(2) application such that the applicant is no longer seeking approval for a method of use claimed by the patent. Once an amendment for the change has been submitted, the 505(b)(2) application will no longer be considered

to contain a paragraph IV certification to the patent. If a final decision finds the patent to be invalid and infringed, an amended certification is not required.

**(ii) After request to remove a patent or patent information from the list.** If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and no ANDA applicant is eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent or patent information will be removed and any applicant with a pending 505(b)(2) application (including a tentatively approved 505(b)(2) application) who has made a certification with respect to such patent must submit an amendment to withdraw its certification. In the amendment, the applicant must state the reason for withdrawing the certification or statement (that the patent has been removed from the list). If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished. A 505(b)(2) applicant is not required to provide or maintain a certification to a patent or patent information that remains listed only for purposes of a first applicant's 180-day exclusivity for its ANDA. Once an amendment to withdraw the certification has been submitted, the 505(b)(2) application will no longer be considered to contain a paragraph IV certification to the patent. If removal of a patent from the list results in there being no patents listed for the listed drug(s) identified in the 505(b)(2) application, the applicant must submit an amended certification reflecting that there are no listed patents.

**(iii) Other amendments.**

**(A)** Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section:

**(1)** An applicant must amend a submitted certification or statement if, at any time before the approval of the 505(b)(2) application, the applicant learns that the submitted certification or statement is no longer accurate; and

**(2)** An applicant must submit an appropriate patent certification or statement under paragraph (i)(1) of this section if, after submission of the 505(b)(2) application, a new patent is issued by the U.S. Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a listed drug relied upon or that claims an approved use for such listed drug for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53.

**(B)** An applicant is not required to submit a supplement to change a submitted certification when information on an otherwise applicable patent is submitted after the approval of the 505(b)(2) application.

**(j) Claimed exclusivity.** A new drug product, upon approval, may be entitled to a period of marketing exclusivity under the provisions of § 314.108. If an applicant believes its drug product is entitled to a period of exclusivity, it must submit with the NDA prior to approval the following information:

**(1)** A statement that the applicant is claiming exclusivity.

**(2)** A reference to the appropriate paragraph under § 314.108 that supports its claim.

**(3)** If the applicant claims exclusivity under § 314.108(b)(2), information to show that, to the best of its knowledge or belief, a drug has not previously been approved under



section 505(b) of the Federal Food, Drug, and Cosmetic Act containing any active moiety in the drug for which the applicant is seeking approval.

- (4) If the applicant claims exclusivity under § 314.108(b)(4) or (b)(5), the following information to show that the NDA contains “new clinical investigations” that are “essential to approval of the NDA or supplement” and were “conducted or sponsored by the applicant:”

(i) **“New clinical investigations.”** A certification that to the best of the applicant’s knowledge each of the clinical investigations included in the NDA meets the definition of “new clinical investigation” set forth in § 314.108(a).

(ii) **“Essential to approval.”** A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval, a certification that the applicant has thoroughly searched the scientific literature and, to the best of the applicant’s knowledge, the list is complete and accurate and, in the applicant’s opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the NDA, and an explanation as to why the studies or reports are insufficient.

(iii) **“Conducted or sponsored by.”** If the applicant was the sponsor named in the Form FDA 1571 for an IND under which the new clinical investigation(s) that is essential to the approval of its NDA was conducted, identification of the IND by number. If the applicant was not the sponsor of the IND under which the clinical investigation(s) was conducted, a certification that the applicant or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its NDA, and information supporting the certification. To demonstrate “substantial support,” an applicant must either provide a certified statement from a certified public accountant that the applicant provided 50 percent or more of the cost of conducting the study or provide an explanation of why FDA should consider the applicant to have conducted or sponsored the study if the applicant’s financial contribution to the study is less than 50 percent or the applicant did not sponsor the investigational new drug. A predecessor in interest is an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug. Purchase of nonexclusive rights to a clinical investigation after it is completed is not sufficient to satisfy this definition.

- (k) **Financial certification or disclosure statement.** The NDA must contain a financial certification or disclosure statement or both as required by part 54 of this chapter.

(l) **Format of an original NDA -**

(1) **Archival copy.** The applicant must submit a complete archival copy of the NDA that contains the information required under paragraphs (a) through (f) of this section. FDA will maintain the archival copy during the review of the NDA to permit individual reviewers to refer to information that is not contained in their particular technical sections of the NDA, to give other agency personnel access to the NDA for official business, and to maintain in one place a complete copy of the NDA. Except as required by paragraph (l)(1)(i) of this section, applicants may submit the archival copy on paper or in electronic

format provided that electronic submissions are made in accordance with part 11 of this chapter.

**(i) Labeling.** The content of labeling required under § 201.100(d)(3) of this chapter (commonly referred to as the package insert or professional labeling), including all text, tables, and figures, must be submitted to the agency in electronic format as described in paragraph (l)(5) of this section. This requirement is in addition to the requirements of paragraph (e)(2)(ii) of this section that copies of the formatted label and all labeling be submitted. Submissions under this paragraph must be made in accordance with part 11 of this chapter, except for the requirements of § 11.10(a), (c) through (h), and (k), and the corresponding requirements of § 11.30.

**(ii)** [Reserved]

**(2) Review copy.** The applicant must submit a review copy of the NDA. Each of the technical sections, described in paragraphs (d)(1) through (6) of this section, in the review copy is required to be separately bound with a copy of the application form required under paragraph (a) of this section and a copy of the summary required under paragraph (c) of this section.

**(3) Field copy.** The applicant must submit a field copy of the NDA that contains the technical section described in paragraph (d)(1) of this section, a copy of the application form required under paragraph (a) of this section, a copy of the summary required under paragraph (c) of this section, and a certification that the field copy is a true copy of the technical section described in paragraph (d)(1) of this section contained in the archival and review copies of the NDA.

**(4) Binding folders.** The applicant may obtain from FDA sufficient folders to bind the archival, the review, and the field copies of the NDA.

**(5) Electronic format submissions.** Electronic format submissions must be in a form that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

## **Data Presentation For FDA Submission**

Data presentation for FDA submission Followings are the ways to present data that facilitate NDA review of submission.

Text exposition

Tabular presentation

### **1. Text exposition**

#### **Content**

Most NDA submission contains enormous amount of data, which cannot be presented entirely within the body of a document. Although the data collected for individual patient 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 specific thesis should be presented within the body of a document rather than placed into remote appendix which will impede the review. Less important data can be summarized briefly and placed in appendices. Data which add nothing to the evaluation of safety or effectiveness of therapeutic agent, need not be presented at all.

## **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.

## **Conciseness**

Following are the way of making NDA submission more concise.

- a. Keep the language simple and straightforward. Simple language is not unscientific; rather it promotes clear and fast understanding. Edit out inflated language. For example, “prior to the initiation of the study” can be changed to much simpler “before the study began”.
- b. Use acronyms and initialisms to speed up the flow of the 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.
- c. 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 deletion of redundant phrases, thus improving the flow of text. D. Correctness: The textual presentation should agree with tabular data in the document; in turn, the tabular data should agree with the data source. When lack of agreement between in-text data and source documents is found, the reviewer will have to spend more time in evaluating the raw data to be sure of conclusion.

## **Consistency**

Consistent punctuation, capitalization, abbreviations, and other styling conventions are much desired in any document.

## **Clarity**

The FDA reviewer should be able to read an application easily and expeditiously. If a particular document is not clear, then FDA reviewer will have the problem for understanding it. Clarity is facilitated by careful attention to the following. Punctuation Sentence structure and length Misplaced modifiers Parallelism.

## **Outline of sections and subsections**

The clear relationship of one section with another is critical to the review of a document. If no definite structure is apparent, the reviewer will become lost. The decimal system is a very popular outlining system; it is easy to use and can be set up automatically in current word processing software application. For e.g., 3.1.2.1.2.1.1.1 is a subsection of 3.1.2.1.2.1.1. H. Indenting : Avoid indenting large sections of the text. Most text should be flush to the left margin with appropriate headers to identify the section. Generally indenting with bullets are useful to break a large sections of text.

## **2. Tabular presentation**

In-text tables should be used to simplify the presentation and substantial reduction in text. Information from tables should not be repeated in the text except as a part of concluding statement about the tabular data.

## **Title**

All tables require concise but descriptive title. Sequence of tables that are similar should identify their differences in the title, such as at the end of the title after a colon. (Treatment related adverse events: by Age... ,by Sex... ,by Race).

## **Data source**

Every table should identify the data source contained in it. This is usually done in the footnote to the table (data source: statistical table 23, volume XX, p. xx). The volume and page numbers will be inserted at the end of the project.

## **Footnotes**

Footnotes should be assigned letters, not symbols or numbers, which can be confused with the data.

## **Orientation**

Portrait tables are always preferable to landscape tables.

## **Order of data presentation**

In multiple tables with similar data, present data in the same order as much as possible. If the first column always has the active drug and the second column has the placebo or comparative agent, then keep this order throughout the tables.

## **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. For e.g., if tabular data represent both evaluable and non evaluable patients who have been either previously treated or previously untreated, place the evaluable patient together rather than present them by previous treatment.

Upon receipt of an NDA, the FDA conducts a review of the application to determine its completeness. Within 60 days, the FDA either accepts the filing or sends the applicant a “refusal-to-file” letter. If the applicant receives a “refusal-to-file” letter, they can request a conference with FDA.

Grounds for refusal to file the application include:

Form FDA 356h has not been completed.

The format of the application is not correct. One or more item is missing from the content as described in the regulations. The manufacturing facilities are not ready for inspection. Complete and accurate translations of all parts of the application not in English are not included.

There are no statements regarding GLP compliance for each of the non clinical studies. There are no statements regarding compliance with IRB and informed consent regulations for each of the clinical studies. The drug product is already covered by an approved NDA or ANDA.

At this stage FDA will send one of three possible action letters to the applicant :

One possibility is a “Not Approvable Letter,” which will list the deficiencies in the NDA and explain why it cannot be approved.

The second possibility is an “Approvable Letter,” which indicates that ultimately the drug product should be approved, but lists minor deficiencies and labeling changes that are needed before an approval. Requests for commitment for post-approval studies may be included.

The third possibility is an “Approval Letter,” it states that the drug is approved. An applicant may receive both an Approvable Letter and Approval Letter. Division director of CDER, signs and approve a letter that the product can be legally marketed, starting on that date onwards.

## Regulatory Agencies that are involved in drug regulation in India

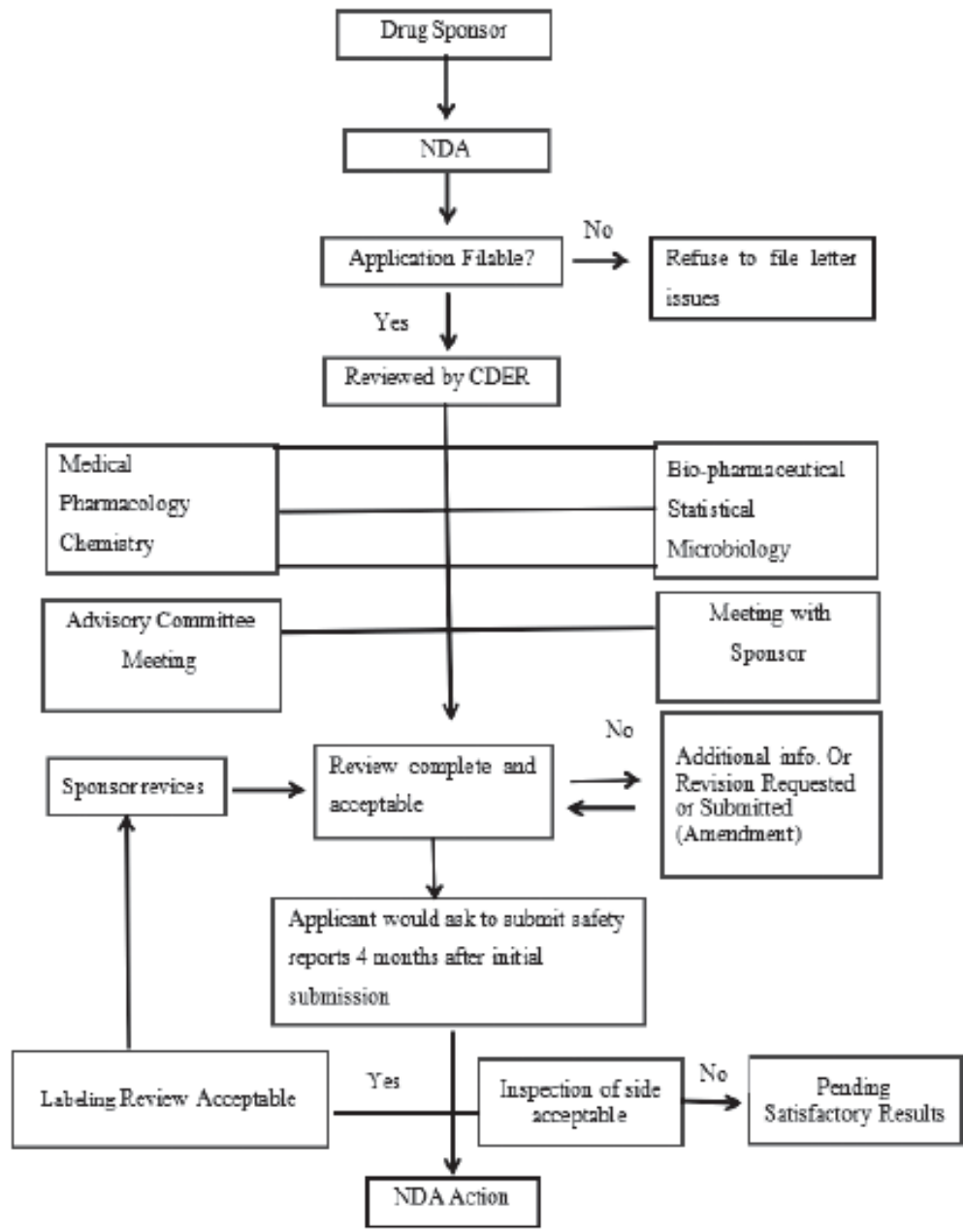


Figure 1- Approval process involved in NDA

### 1. Drug Controller General of India

Clinical Research is regulated in India by Drug Controller General of India (DCGI). The office of DCGI runs under CDSCO. It has main responsibility of regulating clinical trials in India. Matters related to product approval and standards, clinical trials, introduction of new drug, and import licenses of new drugs are handled by DCGI.

### 2. Drugs Technical Advisory Board (DTAB)

It has technical experts and this advice the central and state governments on all technical matters arising out of the enforcement of drug control. No rules can be made by the central government without consulting DTAB board.

### **3. Drugs Consultative Committee**

It has central and state drug control officials as members. Its main function is to ensure the drug control measures and enforce them uniformly over all the states.

### **4. Genetic Engineering approval Committee (GEAC)**

It is authority to approve r-DNA pharmaceuticals products. GEAC's role is to assess the bio-safety/environmental safety aspect of the biotechnological product.

### **Some of the rules & guidelines that should be followed for regulation of drugs in India are**

Drugs and Cosmetics Act 1940 and its rules 1945

Narcotic Drugs and Psychotropic Substances-1985

Drugs Price Control Order 1995

Consumer Protection Act-1986

Factories Act-1948

Law of Contracts (Indian contract Act-1872)

Monopolistic & Restrictive Trade Practices Act-1969

ICH GCP Guidelines

Schedule Y Guidelines

ICMR Guidelines

Registry of Trial

### **Requirements for permission of New Drugs Approval**

The manufacturer / sponsor has to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945.

The document design is as per the International submission requirements of Common Technical Document (CTD) and has five Modules.

#### **Module I**

##### **Administrative/Legal Information**

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

#### **Module II**

##### **Summaries**

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action and proposed clinical use. In general, the introduction should not exceed one page. The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It contains the CTD summaries for quality, safety, efficacy information. This module is very important, as it provides detailed summaries of the various sections of the CTD. These include: A very short introduction. Quality overall summary,

Non clinical overview, Clinical over view, Non clinical written and tabulated summaries for pharmacology, pharmacokinetics, and toxicology.

### **Module III**

#### **Quality information (Chemical, pharmaceutical and biological)**

Information on quality should be presented in the structured format described in the guidance M4Q. This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products. It contains of all of the quality documents for the chemistry, manufacture, and controls of the drug substance and the drug product.

### **Module IV**

#### **Non-clinical information**

Information on safety should be presented in the structured format described in the guidance M4S. The purpose of this section is to present a critical analysis of the non-clinical data pertinent to the safety of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. It gives final copy of all of the final nonclinical study reports.

### **Module V**

#### **Clinical information**

Information on efficacy should be presented in the structured format described in the guidance M4E. It gives clinical summary including biopharmaceutics, pharmacokinetics and pharmacodynamics, clinical pharmacology studies, clinical efficacy, clinical safety, synopses of the individual studies and final copy of detailed clinical study reports.

#### **Preparation of the quality information for drug submission for new drug approval**

- Drug substance (name, manufacturer)
- Characterization (name, manufacturer)
- Physicochemical characterization
- Biological characterization
- Drug product (name, dosage form)
- Control of drug product (name, dosage form)

#### **Appendices**

- Facilities and equipment (name, manufacturer)
- Safety evaluation adventitious agents (name, dosage form, manufacturer).

#### **Application for permission to import New Drug (122-A)**

- a. No new drug shall be imported, except under, and in accordance with, the permission granted by the Licensing Authority as defined in clause (b) of rule 21;
- b. An application for grant of permission to import a new drug shall be made in Form 44 to the Licensing Authority, accompanied by a fee of fifty thousand rupees:

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany



such application shall be fifteen thousand rupees;

Provided further that any application received after one year of the grant of approval for the import and sale of new drug, shall be accompanied by a fee of fifteen thousand rupees and such information and data as required by Appendix 1 or Appendix 1A of Schedule Y, as the case may be.

1. The importer of a new drug when applying for permission under sub-rule (shall submit data as given in Appendix 1 to Schedule Y including the results of local clinical trials carried out in accordance with the guidelines specified in that Schedule and submit the report of such clinical trials in the format given in Appendix II to the said Schedule:

Provided that the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries:

Provided further that the submission of requirements relating to Animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

2. The Licensing Authority, after being satisfied that the drug if permitted to be imported as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, may issue an import permission in Form 45 and/or Form 45 A, subject to the conditions stated therein;

Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission, could be considered.

### **Application for approval to manufacture New Drug other than the drugs classifiable under Schedules C and C (1) (122-B)**

(a) No new drug shall be manufactured for sale unless it is approved by the Licensing Authority as defined in clause (b) of rule 21.

(b) An application for grant of approval to manufacture the new drug and its formulations shall be made in Form 44 to the Licensing Authority as defined in clause (b) of rule 21 and shall be accompanied by a fee of fifty thousand rupees;

Provided that where the application is for permission to import a new drug (bulk drug substance) and grant of approval to manufacture its formulation/s, the fee to accompany such application shall be fifty thousand rupees only;

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany such subsequent application shall be fifteen thousand rupees;

Provided further also that any application received after one year of the grant of approval for the manufacture for sale of the new drug, shall be accompanied by a fee of fifteen thousand rupees and such information and data as required by Appendix I or Appendix I A of Schedule Y, as the case may be.



The manufacturer of a new drug under sub-rule (1) when applying for approval to the licensing authority mentioned in the said sub-rule, shall submit data as given in Appendix I to schedule Y including the results of clinical trials carried out in the country in accordance with the guidelines specified in schedule Y and submit the report of such clinical trials in the format given in Appendix II to the said schedule.

The Licensing Authority as defined in clause (b) of rule 21 after being satisfied that the drug if approved to be manufactured as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, shall issue approval in Form 46 and/or Form 46 A, as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission could be considered.

When applying for approval to manufacture of a new drug under sub-rule (1) or its preparations to the state licensing authority, an applicant shall produce along with his application, evidence that the drug for the manufacture of which application is made has already been approved by the licensing authority mentioned in Rule 21; Provided that the requirement of submitting the result of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries;

Provided further that the submission of requirements relating to Animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

### **Permission to import or manufacture fixed dose combination (122-D)**

An application for permission to import or manufacture fixed dose combination of two or more drugs as defined in clause (c) of rule 122 E shall be made to the Licensing Authority as defined in clause (b) of rule 21 in Form 44, accompanied by a fee of fifteen thousand rupees and shall be accompanied by such information and data as is required in Appendix VI of Schedule Y.

The Licensing Authority after being satisfied that the fixed dose combination, if approved to be imported or manufactured as finished formulation shall be effective and safe for use in the country, shall issue permission in Form 45 or Form 46, as the case may be, subject to the conditions stated there in; Provided that the Licensing Authority shall where the data provided or generated on the fixed dose combination is inadequate, intimate the applicant in writing, and the conditions which shall be satisfied before grant of approval/permission could be considered.

### **Application for permission to conduct clinical trials for new drug(122-D)**

No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any Institution, shall be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority defined in clause (b) of rule 21.

An application for grant of permission to conduct, -

Human clinical trials (Phase-I) on a new drug shall be made to the Licensing Authority in Form 44 accompanied by a fee of fifty thousand rupees and such information and data as required under Schedule Y;

Exploratory clinical trials (Phase-II) on a new drug shall be made on the basis of data emerging

from Phase-I trial, accompanied by a fee of twenty-five thousand rupees;

Confirmatory clinical trials (Phase-III) on a new drug shall be made on the basis of the data emerging from Phase-II and where necessary, data emerging from Phase-I also, and shall be accompanied by a fee of twenty-five thousand rupees:

Provided that no separate fee shall be required to be paid along with application for import/manufacture of a new drug based on successful completion of phases of clinical trials by the applicant.

Provided further that no fee shall be required to be paid along with the application by Central Government or State Government institutes involved in clinical research for conducting trials for academic or research purposes.

The Licensing Authority after being satisfied with the clinical trials, shall grant permission in Form 45 or Form 45A or Form 46 or Form 46-A, as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall, where the data provided on the clinical trials is inadequate, intimate the applicant in writing, within six months, from the date of such intimation or such extended period, not exceeding a further period of six months, as the Licensing Authority may, for reasons to be recorded, in writing, permit, intimating the conditions which shall be satisfied before permission could be considered:

### **Suspension or cancellation of Permission / Approval (122-DB)**

If the importer or manufacturer under this Part fails to comply with any of the conditions of the permission or approval, the Licensing Authority may, after giving an opportunity to show because why such an order should not be passed, by an order in writing stating the reasons there for, suspend or cancel it.

### **Appeal (122-DC)**

Any person aggrieved by an order passed by the Licensing Authority under this Part, may within sixty days from the date of such order, appeal to the Central Government, and the Central Government may after such enquiry into the matter as is considered necessary, may pass such order in relation thereto as it thinks fit.

### **Resources for NDA Submissions**

The following resources have been gathered to provide you with the legal requirements of a new drug application, assistance from CDER to help you meet those requirements, and internal NDA review principles, policies and procedures.

### **Guidance Documents for NDAs**

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidance are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office. For the complete list of CDER guidance, please see the Guidance Index. For information on a specific guidance document, please

contact the originating office.

### **Guidance documents to help prepare NDAs.**

- ❖ Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs and General Considerations
- ❖ Changes to an Approved NDA or ANDA
- ❖ Changes to an Approved NDA or ANDA: Questions and Answers
- ❖ Container Closure Systems for Packaging Human Drugs and Biologics
- ❖ Format and Content of the Microbiology Section of an Application,
- ❖ Format and Content of the Clinical and Statistical Sections of an Application
- ❖ Summary for New Drug and Antibiotic Applications—Format and Content of the Summary for New Drug and Antibiotic Applications
- ❖ Formatting, Assembling and Submitting New Drug and Antibiotic Applications,
- ❖ GUIDELINE FOR SUBMITTING SUPPORTING DOCUMENTATION IN DRUG APPLICATIONS FOR THE MANUFACTURE OF DRUG PRODUCTS
- ❖ NDAs: Impurities in Drug Substances
- ❖ Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application
- ❖ Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application
- ❖ Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- ❖ Drug Master Files: Guidelines
- ❖ FDA IND, NDA, ANDA, or Drug Master File Binders
- ❖ PET Drug Applications - Content and Format for NDAs and ANDAs — 2011

### **Laws, Regulations, Policies and Procedures**

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. With numerous amendments, it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

### **Code of Federal Regulations (CFR)**

The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains all regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.

## **CDER's Manual of Policies and Procedures (MaPPs)**

These documents are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures.

### **MaPPS of particular interest to NDA applicants**

- ❖ Review of the Same Supplemental Change to More than One NDA or ANDA in More Than One Review Division
- ❖ NDAs and BLAs: Filing Review Issues
- ❖ Action Packages for NDAs and Efficacy Supplements
- ❖ Refusal to Accept Application for Filing from Applicants in Arrears
- ❖ Requesting and Accepting Non-Archivable Electronic Material for CDER Applications

### **Prescription Drug User Fee Act (PDUFA)**

On November 21, 1997, The President signed the Food and Drug Administration Modernization Act of 1997. This legislation includes authorization for FDA to continue to collect three types of user fees from applicants who submit certain new drug and biological product applications. FDA was first authorized to collect user fees under the Prescription Drug User Fee Act (PDUFA) of 1992.

- ❖ Prescription Drug User Fee Act Related Documents

### **NDA Forms and Electronic Submissions**

- ❖ Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug for Human Use
- ❖ Form FDA-356h instructions
- ❖ Form FDA-3397. User Fee Cover Sheet
- ❖ Form FDA-3331. New Drug Application Field Report
- ❖ Guidance Documents for Electronic Submissions
- ❖ For more information on electronic submissions, see [Electronic Regulatory Submissions and Review Helpful Links](#).

### **Advisory Committees**

Advisory committees provide independent advice and recommendations to the FDA on scientific and technical matters related to the development and evaluation of products regulated by the Agency. CDER requests advice from advisory committees on a variety of matters, including various aspects of clinical investigations and applications for marketing approval of drug products. Committee members are scientific experts such as physician-researchers and statisticians, as well as representatives of the public, including patients. Although the committees provide recommendations to the Agency, final decisions are made by FDA.

- ❖ FDA Advisory Committees
- ❖ CDER Advisory Committees
- ❖ CFR 21 Part 14 Public Hearing before a Public Advisory Committee. Detailed description of advisory committees from the Code of Federal Regulations.
- ❖ Guidance for Industry: Advisory Committees. Includes information on membership, conflict of interest, scheduling, and action on recommendations.

- ❖ Advisory Committee Meeting Calendar. Several dates have been set aside by CDER advisory committees for possible future meetings. The subject matter and location of the meetings (if they are held) will be published in the Federal Register in the month prior to the meeting date.

## **Approval of new drug in India**

When a company in India wants to manufacture/ import a new drug it has to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population it has to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format.

But a provision is there in Rule- 122A of Drugs and Cosmetics Act 1940 and Rules 1945 that the licensing authority may waive certain trails if he considers that in the interest of public health, he may grant permission for import of new drugs basing on the data of the trials done in other countries. Similarly, there is another provision in Rule- 122A which says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries.

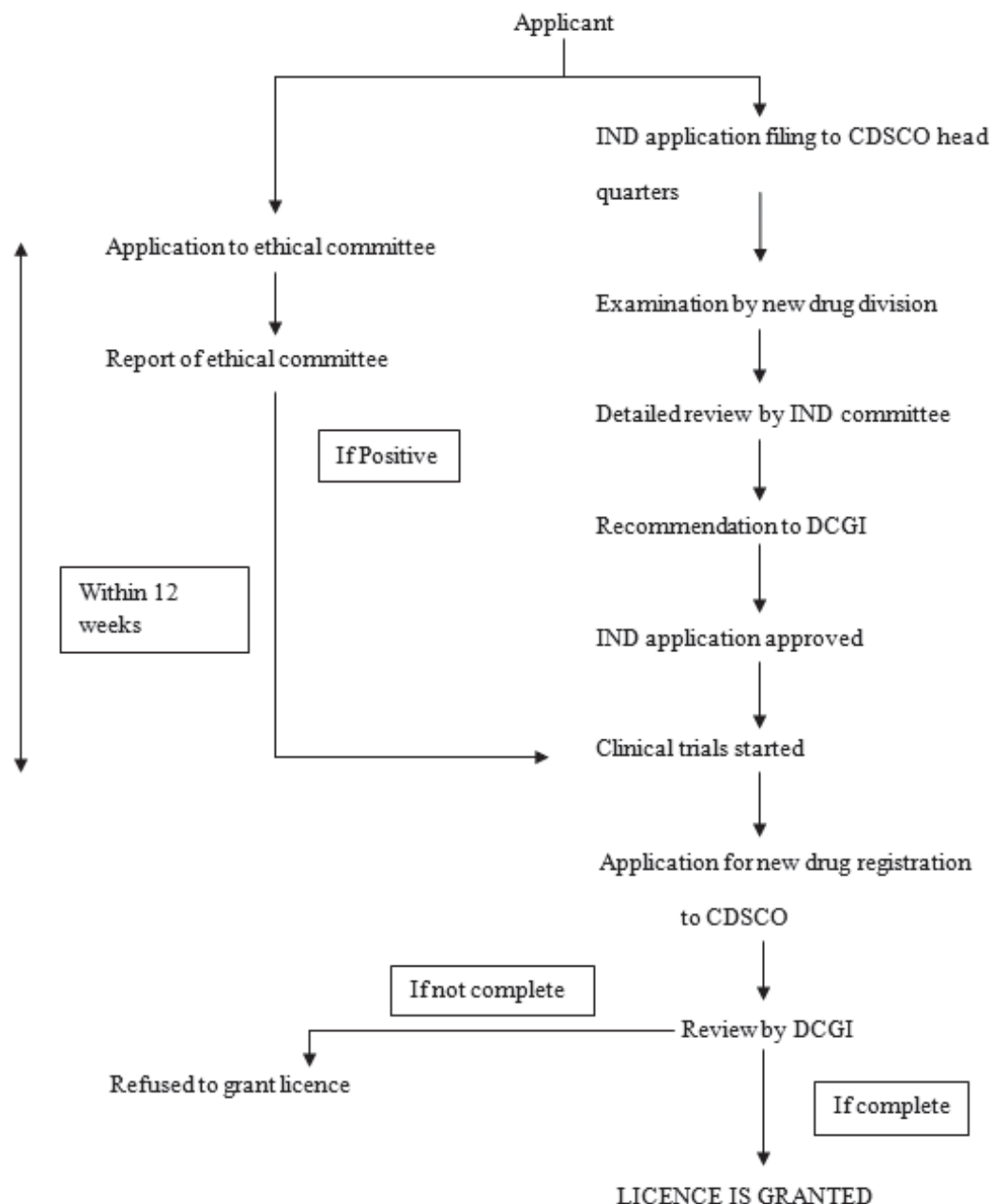
Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required.

Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials.

Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that the licensing authority may require pharmacokinetic studies (Bioequivalence studies) first to show that the data generated in Indian population is equal to data generated abroad and then require him to proceed with Phase III trials.

In summary, the exact requirements of Clinical trials may change from case to case and depend on the extent to which licensing authority is satisfied about its safety and efficacy.

The process of approval of new drug in India is a very complicated process, which should meet necessary requirements along with NDA to FDA. The need of the present work is to study and document the requirements for the process of approval of new drug in India with emphasis on clinical trials as per Drugs Control department, Government of India.



**Figure 2:** Pictorial representation drug approval process in India

## Abbreviated New Drug Application (ANDA)

### Background

An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).



Generic drug applications are termed “abbreviated” because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product performs in the same manner as the innovator drug. One-way applicants demonstrate that a generic product performs in the same way as the innovator drug is to measure the time it takes the generic drug to reach the bloodstream in healthy volunteers. This demonstration of “bioequivalence” gives the rate of absorption, or bio-availability, of the generic drug, which can then be compared to that of the innovator drug. To be approved by FDA, the generic version must deliver the same amount of active ingredients into a patient’s bloodstream in the same amount of time as the innovator drug.

The “Drug Price Competition and Patent Term Restoration Act of 1984,” also known as the Hatch-Waxman Amendments, established bioequivalence as the basis for approving generic copies of drug products. These Amendments permit FDA to approve applications to market generic versions of brand-name drugs without repeating costly and duplicative clinical trials to establish safety and efficacy. Under the Hatch-Waxman Amendments, brand-name companies gained patent term extension to account for the time the patented product is under review by FDA and also gained certain periods of marketing exclusivity. In addition to the ANDA approval pathway, generic drug companies gained the ability to challenge patents in court prior to marketing as well as 180-day generic drug exclusivity.

Through an Abbreviated new drug application (ANDA) process, applicant may get FDA approval for a generic drug without conducting clinical trials if the drug is bioequivalent to the branded (innovator) drug. All generic drugs approved by FDA have the same high quality, strength, purity and stability as brand name drugs.

### Types of ANDA:

**Para I:** A Para I filing for the launch of generic drug is made when the innovator has not made the required information in the Orange book.

**Para II:** A Para II filing is made when the drug is already off patent.

**Para III:** A Para III filing is made when the applicant does not have any plans to sell the generic drug until the original drug is off patent.

**Para IV:** A Para IV filing for the launch of generic drug is made when the applicant believes its product or the use of its product does not infringe on the innovator’s patents or where the applicant believes such patents are not valid or enforceable.

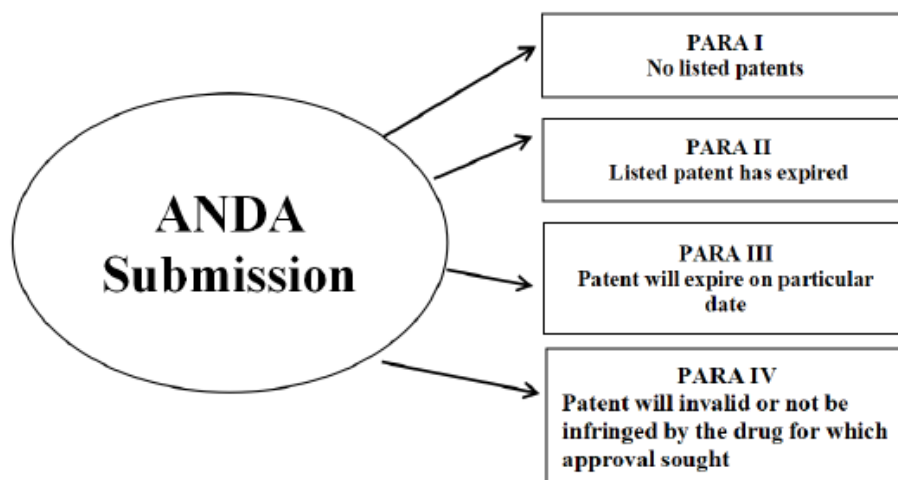


Figure 3 -Types of ANDA

An ANDA certified under paragraphs I or II is approved immediately after meeting all applicable regulatory and scientific (efficacy, safety and bioequivalence) requirements. This means that the generic drugs manufacturer may get immediate approval for manufacturing the generic versions of the branded drugs upon filing an ANDA if, the patent information on the branded drug has not been filed by the branded drug manufacturer or if the patent for the branded drug has expired. A Para III filing is made when the ANDA applicant does not have any plans to sell the generic drug until the original drug is off patent. In case of Para III the application is processed for approval, however its approval status depends upon the product's patent expiry. ANDA approval under Para III certification is made effective from the date of patent expiration.

An ANDA applicant filing a paragraph IV certification must notify the proprietor of the patent. The patent holder may bring a patent infringement suit within 45 days of receiving such notification. If the patent owner timely brings a patent infringement charge against the ANDA applicant, then the USFDA suspends the approval of the ANDA until the date of the court's decision that the listed drug patent is either invalid or not infringed the date on which the listed drug patent expires, if the court finds the listed drug's patent is infringed; or the date that is 30 months from the date the owner of the listed drug's patent received notice of the filing of a Paragraph IV certification. (Subject to modification by the court). This means that for 30 months from the date of receipt of notice of Para VI filing, no ANDA can be approved. In other words, once the branded drug company indicates its intent to begin a patent infringement suit against the generic company as a result of the paragraph IV filing, the USFDA is prohibited from approving the drug in question for thirty months or until such time that the patent is found to be invalid or not infringed. If, prior to the expiration of thirty months, the court holds that the patent is invalid or would not be infringed, then the USFDA approves the ANDA when that decision occurs. Conversely, if the court holds that the patent is valid and would be infringed by the product proposed in the ANDA prior to the expiration of thirty months, then the USFDA does not approve the ANDA until the patent expires.

### **FDA Review Procedure:**

Drugs intended for human use are evaluated by FDA's Center for Drug Evaluation and Research (CDER) to ensure that drugs marketed in the United States are safe and effective. Biological products are evaluated by FDA's Center for Biologics Evaluation and Research.

1. As a part of the review process FDA will send the application of the applicant to OGD/CDER review team for the approval.
2. If the submitted application is not complete or any deficiencies are identified, then "refuse to file letter" is issued by the OGD/CDER to the applicant.
3. In case the application has found complete without any deficiencies then it's accepted & application is then sent to the internal review team for the identification of Bio-Equivalence, Chemistry/Microbiology, Plant inspection & Labeling review issues.
4. If any pending results are found in the application, Bio-Equivalence deficiency letter, & pending satisfactory results are issued accordingly to the applicant.
5. Once the ANDA submission is complete and acceptable without any further queries, the applicant finally receives FDA approval letter.

### **Resources for ANDA Submissions**

The following resources provide ANDA applicants with the statutory and regulatory requirements of an ANDA application, assistance from CDER to help you meet those requirements, and internal ANDA review principles, policies, and procedures. Summary tables, application forms,



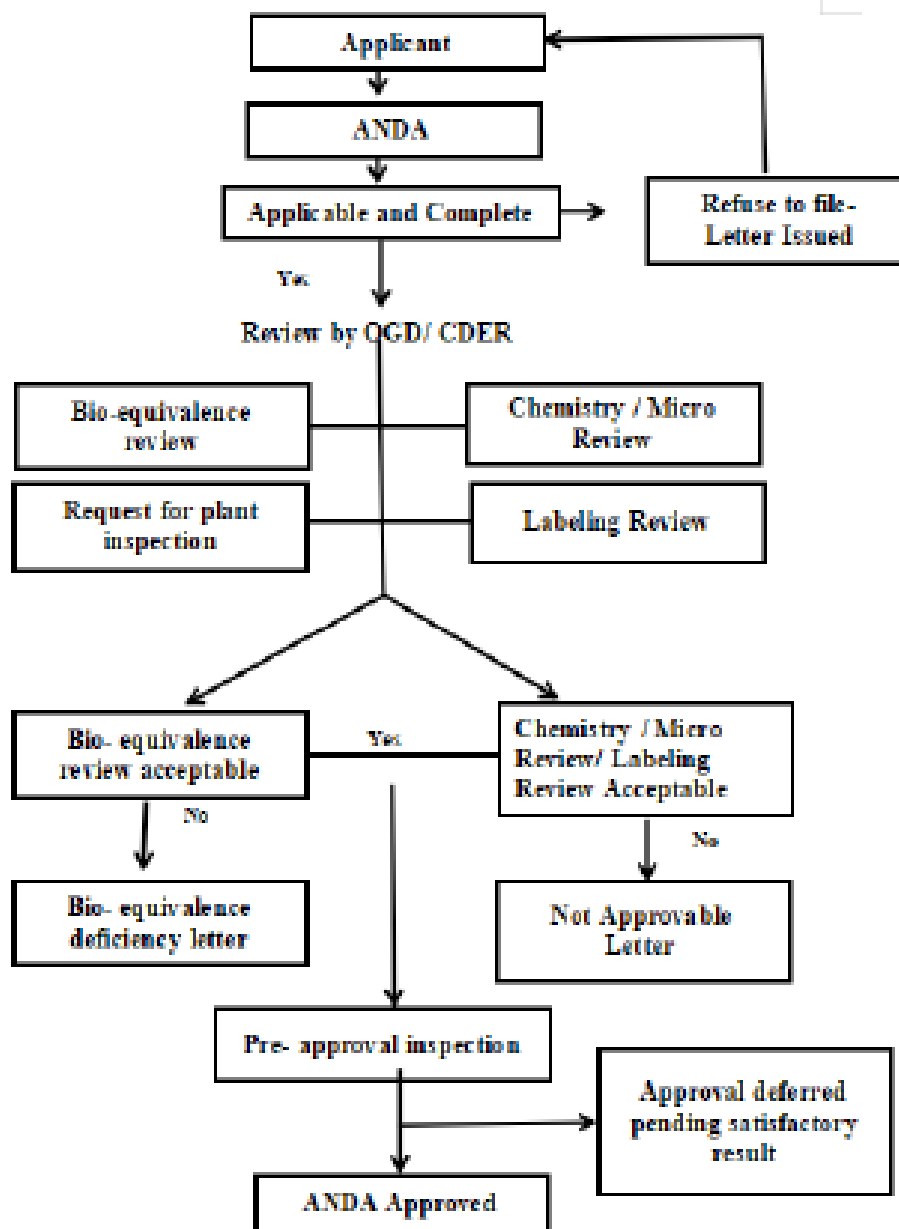


Figure 4- Approval process of ANDA

and other ANDA submission resources are available in ANDA Forms & Submission Requirements.

### Guidance Documents for ANDAs

Guidance documents represent the Agency’s current thinking on a particular topic. These documents provide guidelines for the content, evaluation, and ultimate approval of applications and also to the design, production, manufacturing, and testing of regulated products for FDA review staff, applicants, and ANDA holders.

- ❖ Generic Drugs Guidance (Search “Generics” under topics)
- ❖ Biopharmaceutics Guidance (Search “Biopharmaceutics” under topics)
- ❖ Product-Specific Guidance for Generic Drug Development

### Laws, Regulations, Policies, and Procedures

The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the United

States. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

## **Code of Federal Regulations**

The final regulations published in the Federal Register (a daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the Code of Federal Regulations (CFR). Section 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug applicants that are required under Federal law. The following regulations directly apply to the ANDA process:

21CFR Part 314: Applications for FDA Approval to Market a New Drug

21CFR Part 320: Bioavailability and Bioequivalence Requirements

## **Manual of Policies and Procedures**

CDER's Manual of Policies and Procedures (MAPPs) document internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, both internal and external. Chapter 5200 covers generic drugs processes and activities

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## **Changes to an approved NDA / ANDA**

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### **Background**

This guidance provides recommendations to holders of NDAs and ANDAs who intend to make post approval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act and 314.70 (21 CFR 314.70). It supersedes the guidance of the same title published November 1999. Recommendations are provided for post approval changes in

1. Components and composition
2. Manufacturing sites
3. Manufacturing process
4. Specifications
5. Container closure system, and
6. Labeling, as well as
7. Miscellaneous changes and
8. Multiple related changes.

### **Guidance prepare**

prepared by under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the FDA.

### **Modernization Act**

On November 21, 1997, the President signed the FDA Modernization Act of 1997.

### **Section 116 of the Modernization Act**

Amended the Act by adding section 506A, which provides requirements for making and

reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

## **The FDA has revised its regulations**

on supplements and other changes to an approved application (21 CFR 314.70) to conform to section 506 A of the Act.

To assess the effect of the change on the identity, strength (e.g., assay, content uniformity), Quality (e.g., physical, chemical, and biological properties), Purity (e.g., impurities and degradation products), or Potency (e.g., biological activity, bio-availability, bioequivalence) of a drug product as these factors may relate to the safety or effectiveness of the drug product. v CDER has published guidance, including the SUPAC (scale-up and post approval changes) guidance, that provide recommendations on reporting categories. Reporting categories: This guidance does not provide for components and composition changes. Section 506A of the Act and 314.70(c) provide for two types of changes-being affected supplements while previously there was only one type.

### **A. Major change**

Major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product

Prior Approval Supplement: An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage)

### **B. Moderate change**

Moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. There are two types of moderate change. (314.70(c)(6)). Supplement - Changes Being Affected in 30 Days: requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. } Supplement - Changes Being Affected: FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement.

### **C. Minor change**

Minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next Annual Report

- a. Editorial changes:** in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), (314.70(a)(1)).
- b. Supplement or annual report:** must include a list of all changes. list must be provided in the cover letter (314.70(a)(6)). In annual reports, the list should be included in the summary section (314.81(b)(2)(i)).
- c. An applicant making a change:** to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B))
- d. Code of Federal Regulations:** (e.g., 21 CFR parts 210, 211, 314). Labeling changes under 314.70(c)(6)(iii) must include 12 copies of the final printed labeling (314.70(c)(1)). In accordance with 314.70(a)(4), any labeling change implemented in accordance with 314.70(b) or (c).

## Assessment of the Effects of the Change

The holder of an approved application under section 505 of the Act manufacturing change.

### 1. Conformance to Specifications

A specification is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of drug product. “Acceptance criteria are numerical limits, ranges, or other criteria for the tests described.” Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

### 2. Additional Testing

material affected by manufacturing changes that the applicant performs additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product have been or will be affected.

Evaluation of any changes in the chemical, physical, microbiological, biological, bio-availability, or stability profiles. Type of manufacturing change, the type of drug substance and the effect of the change on the quality of the drug product. For example:

- a. **Evaluation of changes in the impurity:** Toxicology tests to qualify a new impurity.
- b. **Evaluation of the hardness or friability:** Tablet B. Equivalence: When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, and potency of the drug product. Equivalent does not necessarily mean identical. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.
- c. **Adverse Effect:** Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. If an assessment indicates that a change FDA recommends that the change be submitted in a prior approval supplement regardless of the recommended reporting category for the change. For example, a process change recommended for a changes-being-effected-in-30days
- d. **Changes in the qualitative or quantitative formulation:** including inactive ingredients, as provided in the approved application, are considered major changes requiring a prior approval supplement, unless exempted by regulation or guidance (314.70(b)(2)(i)).
- e. **The deletion or reduction of an ingredient:** Intended to affect only the color of the drug product may be reported in an annual report (314.70(d)(2)(ii)).

### 3. Guidance on changes in components and composition

that may be submitted in a changes-being-effected supplement or annual report is not included in this document because of the complexity of the recommendations, but may be covered in one or more guidance documents describing post approval changes (e.g., SUPAC documents).

#### A. General Considerations

CDER must be notified when a manufacturer changes to a manufacturing site that is different from those specified in the approved application (314.70(a)). Sites can include those used by an applicant to

1. Manufacture or process drug products: in-process materials, drug substances, or drug substance intermediates,
2. Package drug products,
3. Label drug products, and
4. Test components, drug product containers, closures, packaging materials, in-process materials, or drug products.
  - a. Testing sites:** Include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing.
  - b. FDA recommends:** That a move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, be submitted as a prior approval supplement if the site does not have a satisfactory CGMP inspection for the type of operation being moved.

## Major Changes

Following are examples of changes.

- 1. Changes that may affect the controlled (or modified) release,**
- 2. Changes that may affect drug product sterility assurance including,**
  - a. Changes in the sterilization method.

These include changes from sterile filtered or aseptic processing to terminal sterilization.

  - b. Addition to an aseptic processing line of new equipment made of different materials
  - c. Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling.
  - d. Changes from bioburden-based terminal sterilization to the use of an overkill process,
  - e. Changes in materials or pore size rating of filters used in aseptic processing.
- 3. Manufacturing process or technology**

### Drug product:

Dry to wet granulation

### Drug substance:

Filtration to centrifugation & Change in the route of synthesis of a drug substance.

Addition of an ink code imprint or in the ink used for an existing imprint code when the ink as changed is not currently used on CDER-approved drug products

Specifications (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in- process materials, container closure systems, and other materials used in the production of a drug substance or drug product. The recommendations in this section also apply to specifications associated with sterility assurance.

The potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction

between the packaging component and the dosage form. In some cases, there may be a substantial potential for adverse effect, regardless of direct drug product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

A change in a drug's labeling includes changes in one of the following:

Package insert

Package labeling

Container label

All promotional labeling and advertising must be promptly revised to be consistent with any labeling change(s) implemented. In addition, "all labeling changes for ANDA drug products must be consistent with section 505(j) of the Act."

Multiple related changes involve various combinations of individual changes. If an applicant has multiple related changes that fall into different recommended reporting categories, "CDER recommends that the submission be in accordance with the reporting category for the individual changes."

As this is simply a summary of the guidance document, we only touched on the "general considerations" that are provided. FDA also provides numerous examples of each type of change that is considered to be major, moderate, and minor.

## **Overview of regulatory authorities of India, United States, European Union, Australia, Japan, Canada (Organization structure and types**

of applications)

## Background

Regulatory affairs in pharmaceutical industry aim at the protection of human health. People and government spent money on drugs because of the role they can play in saving lives, restoring health, preventing diseases and stopping epidemics. But, in order to do so, drug must be safe, effective and of good quality. Since the purpose of drug is to diagnose, prevent or treat diseases or ailments in humans, they are products intimately linked with the advances in research and regulation. The pharmaceutical industry, while pursuing an international market, is obliged to comply with national regulations. So, in this review article, an overview of few drug regulatory agencies of four countries: India, USA, Europe & Japan is covered. Regulatory agencies and organizations play a vital role to meet the requirements of legal procedures related to drug development process in a country. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the drug development, licensing & registration.

Sr. No	Country	Authority
1	India	CDSCO
2	USA	USFDA
3	European Union	EMA
4	Australia	TGA
5	Japan	MHLW
6	CANADA	HEALTH CANADA

## Drug Regulatory Agencies in India

India has emerged as one of the leading markets for pharmaceutical products. Increase in the private health care infrastructure, widening rural markets, and inclusion of newer technologies have placed health care as an independent sector in India. With privatization of health care, the medical devices sector is growing too.

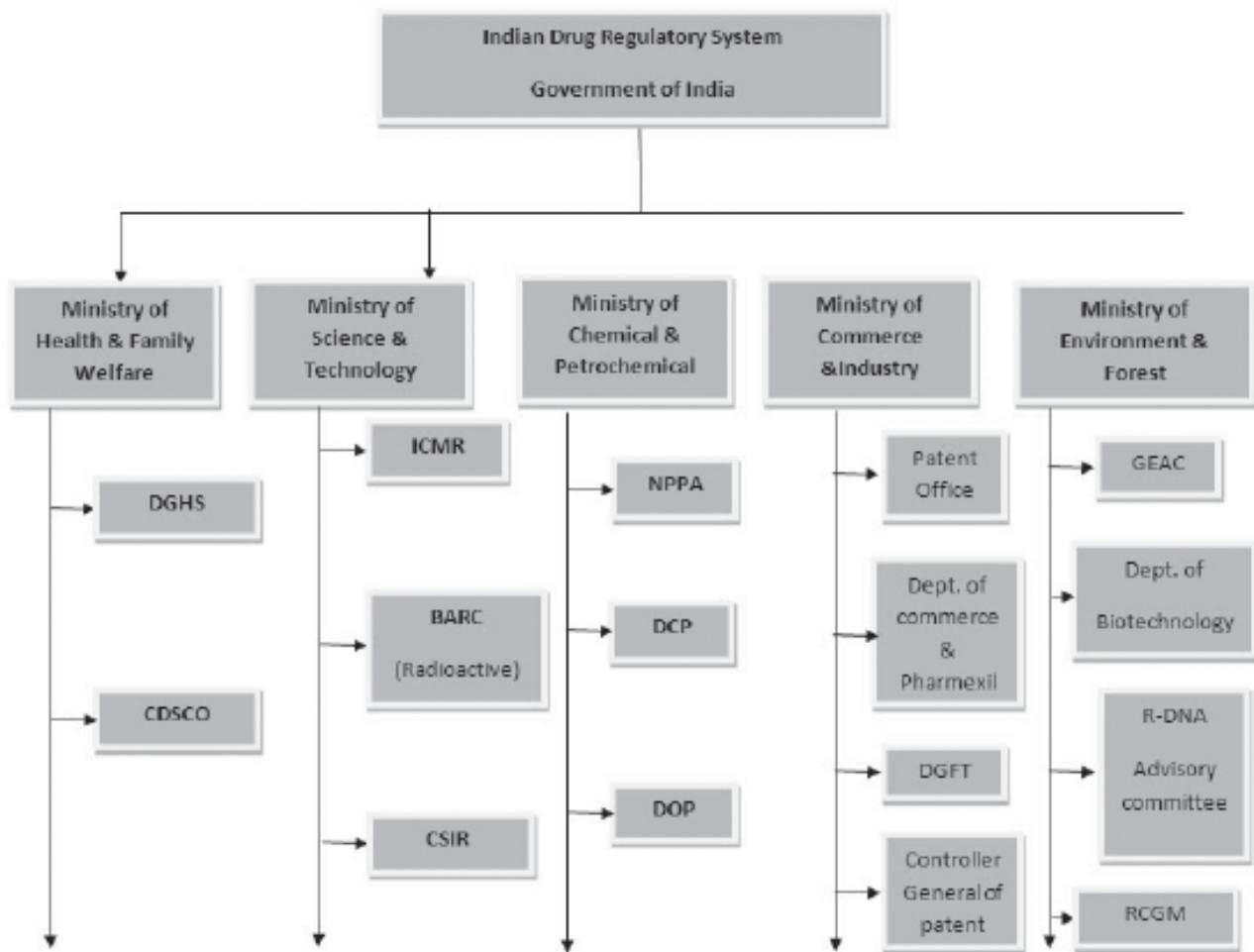
In order to regulate the import, manufacture, distribution and sale of drugs and cosmetics, the Drugs and Cosmetics Act, 1940 (“D&C, Act”) was introduced in India in 1940. However, no separate regulation has been enacted for regulating the import, manufacture, distribution or sale of medical devices in India till date by the Government of India. Drugs and Health is in concurrent list of Indian Constitution. It is governed by both Centre and State Governments under the Drugs & Cosmetics Act, 1940.

### Main Bodies

Central Drug Standard Control

Organization (CDSCO) Ministry of Health & Family Welfare (MHFW)





Indian Council of Medical

Research (ICMR) Indian

Pharmaceutical Association (IPA) Drug Technical Advisory Board (DTAB)

Central Drug Testing Laboratory (CDTL) Indian Pharmacopoeia Commission (IPC)

National Pharmaceutical Pricing Authority (NPPA)

Functions undertaken by Central Government Statutory function laying down standards of drugs, cosmetics, diagnostics and devices. Laying down regulatory measures, amendments to Act and Rules. To regulate market authorization of new drugs. To regulate clinical research in India to approve licenses to manufacture certain categories of drugs as Central License Approving Authority i.e. for Blood Banks, Large Volume Parenteral and Vaccines & Sera. To regulate the standards of imported drugs. Work relating to the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC). Testing of drugs by Central Drugs Labs. Publication of Indian Pharmacopoeia.

### **Central Drugs Standard Control Organization (CDSCO)**

In India, the Central Drugs Standard Control Organization (CDSCO) is the main regulatory body currently regulating import, sale and manufacture of medical devices which have been notified as drugs by virtue of Section 3(b) (IV) of the D&C Act. The CDSCO lays down standards of drugs, cosmetics, diagnostics and devices and issues licenses to drug manufacturers and importers. It also lays down regulatory measures, amendments to Act and Rules and regulates market



authorization of new drugs, clinical research in India and standards of imported drugs etc.

Head quartered in New Delhi, the CDSCO is India's main regulatory body for pharmaceuticals and medical device sand Within the CDSCO, the Drug Controller General of India (DCGI) is responsible for the regulation of pharmaceuticals and medical devices. The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC). Licensing and classification of medical devices are handled by the Central Licensing Approval Authority (CLAA). The CLAA is also responsible for setting and enforcing safety standards, appointing notified bodies to oversee conformity assessment, conducting post- market surveillance and issuing warning sander calls for adverse events. The CDSCO establishes safety, efficacy, and quality standards for pharmaceuticals and medical devices. It publishes and updates the Indian Pharmacopeia, a list of regulated pharmaceuticals and devices. For all drug and device applications, the CDSCO appoints notified bodies to perform conformity assessment procedures, including testing, in order to ensure compliance with their standards. The CDSCO is also divided into several zonal offices which do pre-licensing and post-licensing inspections, post-market surveillance, and recalls when necessary.

In addition to its regulatory functions, the CDSCO offers technical guidance, trains regulatory officials and analysts, and monitors adverse events. The CDSCO works with the World Health Organization to promote Good Manufacturing Practice (GMP) and international regulatory harmony.

### **National Institute of Health and Family Welfare (NIHFW)**

NIHFW is an Apex Technical Institute, funded by Ministry of Health and Family Welfare, for promotion of health and family welfare programmers in the country through education, training, research, evaluation, consultancy and specialized services. The NIHFW was established on March 9, 1977 by a merger of the National Institute of Health Administration and Education (NIHAE) with the National Institute of Family Planning (NIFP).

List of Governing Body Members of NIHFW 18 members

1 Chairman (ex-officio)

1 Vice Chairman (ex-officio) 9 Member (ex-officio)

6 Member

1 Member Secretary (ex-officio)

### **Activities and Responsibilities**

Measuring weight of children to assess the nutritional status. Assessment of diseases like level of anemia. Testing of foodmaterial like cooking salt for level, iodine. To release fund on the advice of the Ministry. It is responsible for all governmental programs relating to family planning in India.

### **Drug technical advisory board(DTAB)**

The Central Government constitute a Board (to be called the Drugs Technical Advisory Board) to advise the Central Government and the State Governments on technical matters arising out of the administration of D&C, Act 1940 List of Governing Body Members of NIHFW:18 Members

10ex-officioMembers

5NominatedMembers

5 Elected Members

### **Activities and responsibilities**

Its advices matter related to Drugs. The nominated and elected members of the Board shall hold office for three years, but shall be eligible for re-nomination and re-election. The Board may, subject to the previous approval of the Central Government, make bye-laws fixing a quorum and regulating its own procedure.

### **Central drug testing laboratory (CDTL)**

The central drug laboratory, Kolkata is national statutory laboratory of the Government of India for quality control of drug and cosmetic and established under the D&C act, 1940. Oldest quality control laboratory of the drug control authorities in India. Function under the director general of Health Services in the Ministry of Health and Family Welfare.

### **Composition**

Indian Pharmacopoeia Commission (IPC) General Body 19Members

Governing Body 10 Members Scientific Body 23 Experts

CIPL Lab IPC Secretariat Indian Pharmacopoeia was prepared by Indian Pharmacopoeia Commission (IPC)

### **Activities and responsibilities**

Development of comprehensive monographs. Accord priority to monographs of drugs included in the national Essential Drug List and their dosage forms. Preparation of mono graph for products that have normally been in the market for not less than 2 years. Collaborate with pharmacopoeias like the BP, USP, JP and International Pharmacopoeia with a view to harmonizing with global standards.

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## **Drug regulatory agencies in USA**

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### **USFDA**

The Food and Drug Administration (FDA) National Institutes of Health (NIH) Centers for Disease Control and Prevention Department of Health and Human Services (DHHS) Fed World - US Government Information National Centre for Complementary and Alternative Medicine (NCCAM) National Centre for Infectious Diseases (NCID) National Library of Medicine National Science Foundation Office of Disease Prevention.

The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services. It consists of six product centers, one research Centre, and two offices. FDA's responsibilities extend to the 50 United States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other U.S. territories and possessions. Food and Drug Administration 10903 New Hampshire Ave Silver Spring, MD20993-0002

The Food and Drug Modernization Act states that the FDA has 4 roles:

To promote health by reviewing research and approving new products.

To ensure foods and drugs are safe and properly labelled.

To work with other nations to “reduce the burden of regulation”.

To cooperate with scientific experts and consumers to effectively carry out these obligations

The FDA is led by the Commissioner of Food and Drugs, who is appointed by the President and confirmed by the Senate.

FDA is responsible for Protecting the public health by assuring that foods are safe, wholesome, sanitary and properly labelled; Assuring human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective Protecting the public from electronic product radiation Assuring cosmetic sand dietary supplements are safe and properly labelled Regulating tobacco products Advancing the public health by helping to speed product innovations Helping the public get the accurate science-based information they need to use medicines, devices, and foods to improve their health Initiation of a Recall. Includes voluntary, FDA requested, and FDA mandated.

FDA is responsible for: protecting the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products, medical devices, our nation's food supply, cosmetics, dietary supplements, and products that give off radiation regulating tobacco products advancing the public health by helping to speed product innovations helping the public get the accurate, science-based information they need to use medicines and foods to improve their health. FDA is responsible for Protecting the public health by assuring that foods are safe, wholesome, sanitary and properly labelled; vaccines and other biological products and medical devices intended for human use are safe and effective. Protecting the public from electronic product radiation Assuring cosmetics and dietary supplements are safe and properly labelled Regulating tobacco products Advancing the public health by helping to speed product innovations Helping the public get the accurate science-based information they need to use medicines, devices, and foods to improve their health Initiation of a Recall. Includes voluntary, FDA requested and FDA mandated.

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## **Drug regulatory agencies in Europe**

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### **European Medicines Agency (EMA)**

EMA is a European agency for the evaluation of medicinal product. EMA was setup in 1995. From 1995 to 2004, EMA was known as European agency for the evaluation of medicinal product. The European Medicines Agency (EMA) is a decentralized body of the European Union, located in London Mission: to foster scientific excellence in evaluation and supervision of medicines.

### **Activities of EMA**

Provides independent, science-based recommendations on the quality, safety and efficacy of medicines. Applies efficient and transparent evaluation procedures to help bring new medicines to the market. Implements measures for continuously supervising the quality, safety and efficacy of authorized medicines. Provides scientific advice to stimulate the development and improve the availability of innovative new medicines. Recommend safe limits for residues of veterinary medicines used in food-producing animals. Publishes impartial and comprehensible information about medicine sand their use; develops best practice for medicines evaluation and supervision in Europe, and contributes alongside the Member States and the European Commission to the harmonization of regulatory standards at the international level. European Directorate for the Quality of Medicines & Health Care the EDQM (Council of Europe) is a key European Organization involved in Harmonization & Co-ordination of Standardization, Regulation & Quality Control of Medicines, Blood Transfusion, Organ Transplantation, Pharmaceutical sand Pharmaceutical Care. In 1996 The European Directorate for the Quality of Medicines (EDQM) is created. EMA is a

European agency for the evaluation of medicinal product. EMA was set up in 1995. From 1995 to 2004, EMA was known as European agency for the evaluation of medicinal product. The European Medicines Agency (EMA) is a decentralized body of the European Union, located in London  
Mission: to foster scientific excellence in evaluation and supervision of medicines. Office of executive director Executive director Legal service Senior medical officer Internal audit Information and communication veterinary medicines and product data management Patient health protection Human medicines development and evaluation

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## **Drug regulatory agencies in japan**

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### **Ministry of Health, Labor, and Welfare (MHLW)**

The Ministry of Health, Labour, and Welfare (MHLW) was established by a merger of the Ministry of Health and Welfare (MHW) and the Ministry of Labour, on January 6, 2001. The MHLW, which was originally established in 1938, has been in charge of the improvement and promotion of social welfare, social security and public health, and the new organization has the same tasks. It consists of the ministry proper, affiliated institutions, councils, local branches, and an external organization.

MHLW Social insurance agency Ministry proper Minister's secretariat Health policy bureau Health service bureau PFSB Social welfare & war victim's relief bureau Health and welfare bureau for elderly Equal employment children & family bureau Insurance bureau Pension bureau Director general for policy planning. Services for persons with disabilities Social Security: Pension systems that will ensure income in elderly age Long term insurance to provide nursing care services Public assistance systems that guarantee minimum standards

### **Function of MHLW**

Public Hygiene: Appropriate medical services for diseases & injuries ensuring the safety of food, Water and medical supplies Research into health science in order to make technological advances Maternal and child health Job Security: Promotion of employment Labor of elderly people Employment of persons with disabilities Management of the employment insurance system

Human Resources Development: Promotion of human resources development that reacts to changes in the industrial system Encouragement of worker's skill development under their own initiative Development of skilled human resources that support industrial progress

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## **Regulatory process for drug in Canada**

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The exhibit shows the steps in the regulatory process for drugs in Canada, from pre-market to post-market. The pre-market part of the process starts with pre-clinical studies.

The steps are

- Pre-clinical studies
- Clinical trials
- Regulatory product submission
- Submission review
- Market authorization decision

Public access

Surveillance, inspection, and investigation

The post-market part of the process begins with surveillance, inspection, and investigation when a drug has been made accessible to the public.

## **Submission type and their description**

Cosmetic

All cosmetics sold in Canada must be safe to use and must not pose any health risk. They must meet the requirements of the Food and Drugs Act and the Cosmetic Regulations.

Under the Food and Drugs Act, a cosmetic includes “any substance or mixture of substances, manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth and includes deodorants and perfumes.” This includes cosmetics used by professional esthetic services, bulk institutional products (such as hand soap in school rest rooms), as well as “handmade” cosmetics sold at craft sales or home- based businesses.

The Cosmetic Regulations and the Food and Drugs Act require that cosmetics sold in Canada be manufactured, prepared, preserved, packed and stored under sanitary conditions. The manufacturer and importer must notify Health Canada that it is selling the product and provide a list of the product’s ingredients.

## **Definitions**

### **1. cosmetic (Section 2 of the Food and Drugs Act)**

any substance or mixture of substances manufactured, sold or represented for use in cleaning, improving or altering the complexion, skin, hair or teeth, and includes deodorants and perfumes.

### **2. drug (Section 2 of the Food and Drugs Act)**

Includes any substance or mixture of substances manufactured, sold or represented for use in

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
- (b) restoring, correcting or modifying organic functions in human beings or animals, or
- (c) disinfection in premises in which food is manufactured, prepared or kept;

### **3. natural health product (Section 1 of the Natural Health Products Regulations pursuant to the Food and Drugs Act)**

A subset of drugs pertaining to medicinal ingredients of natural origin, defined in the Natural Health Products Regulations as “a substance set out in Schedule 1 or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;
- (b) restoring or correcting organic functions in humans; or
- (c) Modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

### **4. personal care product (PCP):**

For the purposes of this document, defined as a substance or mixture of substances which is

generally recognized by the public for use in daily cleansing or grooming. Personal care products may fall into one of three regulatory categories in Canada: cosmetics, drugs or natural health products.

## **5. product at the cosmetic-drug interface (PCDI):**

A subset of personal care products, which are not easily distinguished as either a drug or cosmetic, as defined in the Food and Drugs Act.

The following are the programs within Health Canada that regulate personal care products.

NHPD: Natural Health Products Directorate (Health Products and Food Branch)

PSD: Product Safety Directorate (Healthy Environments and Consumer Safety Branch)

TPD: Therapeutic Products Directorate (Health Products and Food Branch)

## **Key features of cosmetic regulations**

### **Main features CANADA**

Manufacturer has full responsibility for safety of products Yes In market control by authorities Yes Freedom to use any distribution channel Yes Notification of products Mandatory notification of product name and function, plus quantitative or semi quantitative ingredients list to be notified 10 days at least after placing the product on the market Quantity labeling Metric labeling mandatory. Non-metric labeling allowed as a supplement Identity of producer/importer on the labels Name and address of manufacturer or dealer. Non-Canadian address is accepted.

Please note that test-marketed cosmetics must meet all requirements of the Food and Drugs Act and the Cosmetic Regulations. There are no exemptions for test-marketing.

The completed Cosmetic Notification Form (CNF) provides specific product information to Health Canada, including: ü address and contact information of the manufacturer(s), importer(s), distributor(s), and formulator(s) ü function of the cosmetic ü form of the cosmetic (for example, cream and gel) ü ingredients of the cosmetic ü concentration of each ingredient.

There is no fee associated with the cosmetic notification process.

The personal information provided to Health Canada is protected under the provisions of the Privacy Act.

Submission of the CNF does not constitute approval for sale by Health Canada, agreement that the product is classified as a cosmetic nor that the product complies with all legislative requirements. Manufacturers and importers are responsible for making sure their cosmetics meet the requirements of the Food and Drugs Act and its Cosmetic Regulations.

If there are concerns with a submitted notification or product (for example: unknown ingredients, missing information, safety issues, improper classification, etc.) Health Canada will inform the responsible company of those concerns. Failure to respond may result in compliance action.

Examples of cosmetics

- ❖ soaps
- ❖ artificial nail builders
- ❖ adhesives such as for artificial nails, hair extensions, etc.
- ❖ moisturizers • tinted moisturizers (concealer)
- ❖ tattoo inks



- ❖ makeup products
- ❖ tooth whiteners
- ❖ cleansing wipes
- ❖ feminine douches
- ❖ Examples of products that are not considered cosmetic
- ❖ sunscreens (including makeup products with SPF)
- ❖ acne treatment
- ❖ skin whiteners or lighteners
- ❖ denture cleaners
- ❖ hand sanitizers
- ❖ artificial nails and hair extensions
- ❖ laser treatment hair removers
- ❖ collagen or “Botox” injections
- ❖ insect repellents
- ❖ oral supplements
- ❖ room or fabric sprays
- ❖ non-prescription contact lenses

### **Information on label**

- ❖ This guide covers three aspects of information appearing on the labels of cosmetic products:
- ❖ the classification of cosmetic products (see section 3).
- ❖ required declarations that must appear on a label. These include:
- ❖ product identity (see section 4),
- ❖ net quantity (see section 5),
- ❖ name and address of the manufacturer (see definition) (see section 6),
- ❖ avoidable hazards and cautions (see section 7), and
- ❖ Ingredients (see section 8).
- ❖ sources of additional information concerning labelling requirements

### **Natural health products**

Natural health products (NHPs) are naturally occurring substances that are used to restore or maintain good health. They are often made from plants, but can also be made from animals, microorganisms and marine sources. They come in a wide variety of forms like tablets, capsules, tinctures, solutions, creams, ointments and drops.

Natural health products, often called “complementary” or “alternative” medicines, include: vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines like traditional Chinese and Ayurvedic (East Indian) medicines, Probiotics, other products like amino acids and essential fatty acids

### **Product authorization**

To be licensed in Canada, natural health products must be safe, effective, of high quality

and carry detailed label information to let people make safe and informed choices.

You can identify products that have been licensed for sale in Canada by looking for the eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) on the label.

A NPN or DIN-HM means that the product has been authorized for sale in Canada and is safe and effective when used according to the instructions on the label.

To be legally sold in Canada, all-natural health products must have a product license, and the Canadian sites that manufacture, package, label and import these products must have site licenses.

To get product and site licenses, specific labelling and packaging requirements must be met, good manufacturing practices must be followed, and proper safety and efficacy evidence must be provided.

#### Product licensing

All-natural health products must have a product license before they can be sold in Canada. To get a license, applicants must give detailed information about the product to Health Canada, including: medicinal ingredients, source, dose, potency, non-medicinal ingredients and recommended use(s).

Once Health Canada has assessed a product and decided it is safe, effective and of high quality, it issues a product license along with an eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM), which must appear on the label. This number lets you know that the product has been reviewed and approved by Health Canada.

### **Labeling**

All NHPs must meet specific labelling requirements, to help you make safe and informed choices about the NHPs you choose to use. Information required on NHP labels includes:

product name, product license number, quantity of product in the bottle, complete list of medicinal and non-medicinal ingredients, recommended use (including purpose or health claim, route of administration and dose), any cautionary statements, warnings, contra-indications and possible adverse reactions associated with the product any special storage condition.





**CHAPTER 01**



**Registration of Indian drug product in over-seas market**

**Procedure for export of pharmaceutical products**

**Technical documentation, Drug Master Files (DMF)**

**Common Technical Document (CTD)**

**Electronic Common Technical 163 Document (eCTD)**

**ASEAN Common Technical Document (ACTD)research**



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**Procedure for export of pharmaceutical products****Background**

India occupies a third largest position in the world in the field of Pharmaceutical industry. These industries are regulated by the Ministry of Health & Family Welfare and Ministry of Chemical & Fertilizers. Despite of its position in Pharmaceutical market and its growing economy, a well sophisticated Research and Development is not affordable due to various reasons. To overcome this pitfall, India opens up its pharmaceutical market to MNC's and it encourages the trading of the drug in and out of the country. Most of the drugs for the Indian market are imported from the European Union followed by North America and Asia. India has a special policy for the purpose of Import and Export called as "EXIM" policy. This policy gives way to quantitative as well as qualitative improvements in the field of Research and Development activities.

The Central Drugs Standard Control Organization (CDSCO) regulates the import and export of the drugs in the country, through 11 Port offices located in different parts of the country. CDSCO regulates the manufacture, sale, import, export, and clinical research of drugs in India by the following rules and acts.

1. Drugs and Cosmetics act, 1940 and Rules, 1945.
2. Pharmacy act, 1948
3. Drugs and Magic Remedies act, 1954.
4. Medicinal and Toilet Preparation act, 1956.
5. Narcotic and Psychotropic Substances act, 1985.
6. The Drugs (Prices Control) order, 1995.

The CDSCO also work through state authorities. While, the central authorities are responsible for approval of new drugs, clinical trials in the country; laying down the standards for the drugs control over the quality of imported drugs coordination of the state drug control organizations; the state authorities regulates manufacture, sale and distribution of drugs, licensing drug testing laboratories, approving drug formulations for manufacture, carrying out pre and post licensing inspections, for the drugs manufactured and marketed in the respective states.

The new patent regime has ushered in the era of product patents for the pharmaceutical sector, in line with the obligations under the World Trade Organization (WTO) and Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement. As a result, the Indian pharmaceutical industry has become self-reliant in several areas and has developed a sounder and technologically advanced R&D segment.

The industry offers several opportunities for investments and trade owing to the following advantageous features:

- ❖ Self-reliance displayed by the production of 70% of bulk drugs and almost the entire requirement of formulations within the country;
- ❖ Low cost of production and R & D of quality bulk drugs and formulation s

- ❖ Strong scientific, innovative and technical manpower
- ❖ Increasing balance of trade in pharma sector.
- ❖ Efficient and cost-effective source for producing generic drugs, especially the drugs going off patent in the next five years.
- ❖ Excellent center for clinical trials in view of the diversity in population.
- ❖ Fast growing biotech industry which has great potential in the international market.

Apart from its strength in manufacturing and exporting allopathic medicines, the systems of medicines like Ayurveda, Unani, Siddha, Yoga, Naturopathy and Homeopathy are also prevalent in the country.

## **Rules Related to Export of Drugs from India**

### **A) Rule 94: Packing and labelling of drugs other than Homeopathic Medicines:**

1. Labels on packages or containers of drugs for export shall be adapted to meet the specific requirements of the law of the Country, to which the drug is to be exported,

Name of the drug

The name, address of the manufacturer and the number of the license under which the drug has been manufactured

Batch or lot number

Date of expiry

The provisions of Rules 96 to 101 inclusive, shall not apply to a medicine made up ready for treatment, whether after or without dilution, which is supplied on the prescription of a registered practitioner provided that:

The medicine is labelled with the following particulars:

The name and address of the supplier;

The name of the patient and the quantity of the medicine;

The number representing serial number of the entry in the prescription register;

The dose, if the medicine is for internal use;

The words -FOR EXTERNAL USE ONLY shall be printed on the label if the medicine is for external application.

### **B) Rule 96: Manner of Labeling**

The following particulars shall be either printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container of any drug and on every other covering in which the container is packed, namely:

- a. for drugs included in the Schedule F or Schedule F (1), the name given therein; for drugs included in the pharmacopoeias and official compendia of drug standards prescribed in Rule 124, the name or synonym specified in the respective official pharmacopoeias and official compendia of drug standards followed by the letters I.P., or, as the case may be, by the recognized abbreviations of the respective official pharmacopoeias and official compendia of drug standards;

- b. for drugs included in the National Formulary of India, the name or synonym specified therein followed by the letters N.F.I.; for other drugs, the international non-proprietary name, if any, published by the World Health Organization or not Published, the name descriptive of the true nature or origin of the substance.

### **Guidelines for the Export of Drug issued by Ministry of Health and Family Welfare**

During the issue of NOC's for manufacture of new (Unapproved) drug solely for export, the following conditions shall be taken into consideration:

1. The application shall provide copy of valid export order and NOC will be issued on a case by case basis against each such order.
2. The applicant shall identify the premises where the drug will be manufactured for export.

The applicant should mention whether the batch to be exported has undergone Quality control testing or shall be tested at the destined site.

The applicant shall ensure that the drug(s) manufactured on the basis of NOC given as per the first condition and it is exported and that no part of it is diverted for domestic sale in India.

The applicant shall make available for inspection of the appropriate authorities, on completion of the export orders, information regarding each consignment dispatched, remaining stock of drug and related raw materials and intermediates in hand.

The applicant shall ensure physical destruction of all un exported quantity of drugs. This should be included as a condition of manufacturing license issued to the applicant by the State licensing authority.

The applicant shall ensure that the drug for which NOC has been given shall cease to be manufactured or exported if the drug is prohibited in future in the country or in the importing country.

### **Requirement for Common Submission Format for Issue of NOC for Export**

The following documents are required in the following manner and order for the issue No Objection Certificate (NOC) for export of drugs from India:

#### **1. Covering letter**

Purchase Order: Order from the foreign buyer either in the name of the manufacturer or trader with the list of products to be exported clearly indicating name of the drug, dosage form, composition and strength pack size duly signed by the competent authority with specific destination point of the importing country. It should be signed by the authority with a valid purchase order no. and recent date not more than 6 months prior to the application made by the firm.

#### **2. Manufacturing License**

Performa Invoice: A copy of Performa invoice from the importing country should accompany with application for import of unapproved Active Pharmaceutical Ingredients, used in the drug formulation, it shall be duly signed by the competent authority.

### **3. Registration Certificate**

Registration certificate required for Common Submission Format for Issue of NOC for Export

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## **Technical documentation**

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### **Background**

The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD - Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.

The CTD is organized into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. In July 2003, the CTD became the mandatory format for new drug applications in the EU and Japan, and the strongly recommended format of choice for NDAs submitted to FDA, United States.

### **Common Technical Document (CTD) for Dossiers**

Technical Document (CTD) is a set of specifications for application dossier for the registration of pharmaceutical products in Europe, Japan and the United States. Common Technical Documents or CTDs are critical sets of information of a new drug that comprise the application dossier. The application dossier is then submitted for the purpose of obtaining approval by regional regulatory authorities before the drug can undergo clinical trials and subsequently be introduced in the market. These regional regulatory organizations include the Food and Drug Administration, or the FDA for the United States of America, the European Medicines Agency, or the EMA for Europe, and the Ministry of Health, Labour, and Welfare for Japan.

Before these drugs regulatory organizations can receive and review the application dossiers on the new drugs, the application dossiers need to be prepared in adherence to a format that is globally agreed upon. The implementation of this standardized format for CTDs are handled by the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Each CTD is segmented into five modules:

1. Administrative and prescribing information
2. Overview and summary of pharmaceutical drugs
3. Quality (pharmaceutical documentation)
4. Pre-clinical(Pharmacology/Toxicology)
5. Clinical (Efficacy and Safety)

#### **A. Module 1**

Each of these modules contain subheadings that are standardized for all jurisdictions of regulation by the respective regulatory organizations, although the information contained in the first module, is specific to the federal requirements of each of the organizations, and contains information pertaining to the application forms and the proposal on the labeling of

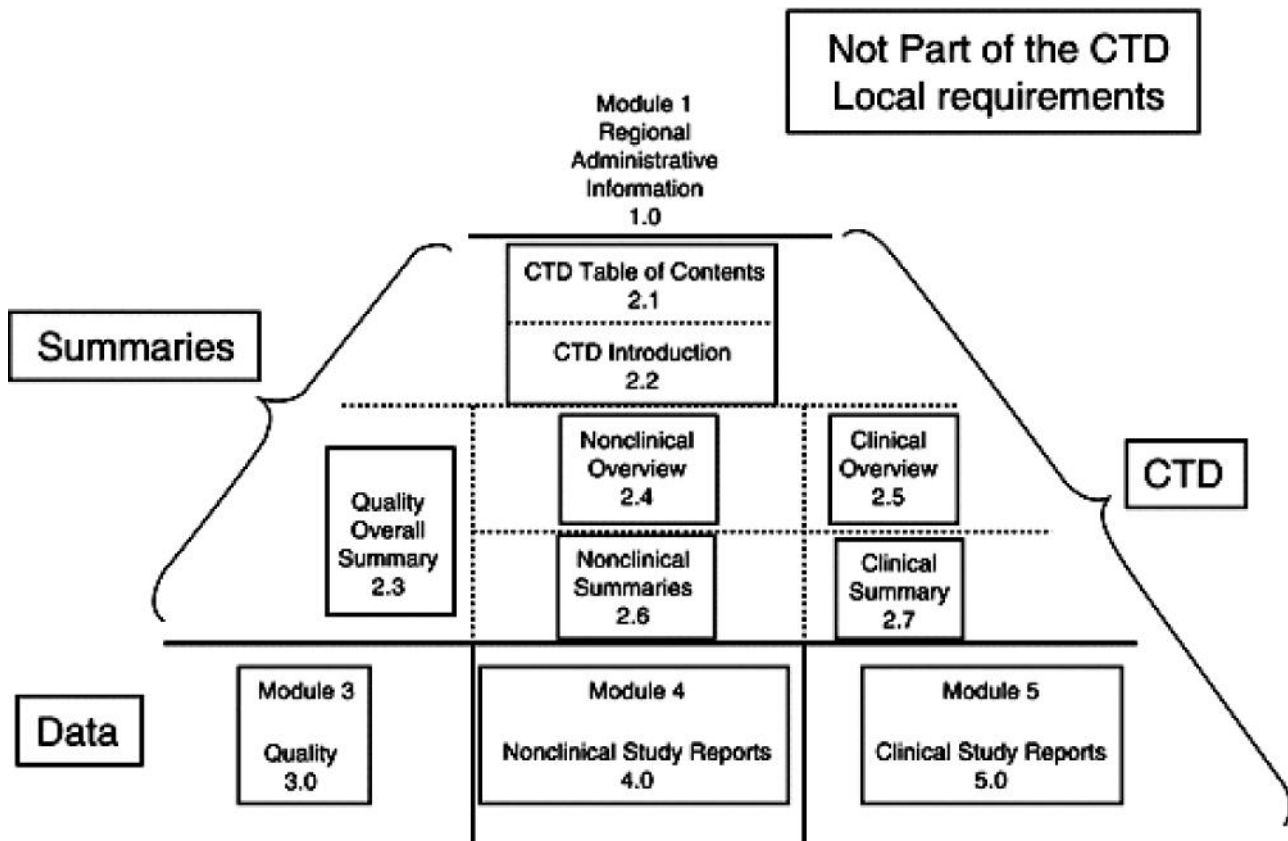


Figure 1- Module of CTD

the drug in question. Apart from the US, Europe, and Japan, Canada and Switzerland have also come to adopt the CTD format. Today, the CTD format remains the most preferred format in the preparation of application dossiers for new drug applications for the FDA, EMA, and the Ministry of Health, Labour, and Welfare in Japan.

## B. Module 2

Module 2 of the CTDs includes summaries containing an overview of the pharmaceutical drug, and how the drug works. This can refer to the pharmacological category the drug belongs to, how it can take effect in the body, and what is the recommended clinical use of the drug. Hence, Module 2 will comprise of information that speaks of the quality of the drug, both clinically and non-clinically.

Related : Abbreviated New Drug Application (ANDA)

## C. Module 3

Module 3 of the CTDs is dedicated to elaborating on the quality control aspects of developing and testing the drug, namely in the chemistry, manufacturing, and controls of the formulating the drug. Module 3 of the registration dossier will contain this information in the same sequence and will be uniformly presented with a table of contents, indicating subheadings on Drug Substance, and Drug Product. There will also be various other appendices on specific aspects of the drug, such as the synthesis of the drug substance, manufacture of the drug product, and container closure.

## D. Module 4 and Module 5

Module 4 and Module 5 both contain reports, but of non-clinical and clinical studies



respectively. The non-clinical study reports in Module 4 are prepared based on the meticulous evaluation of the proposed drug's pharmacologic, pharmacokinetic, and toxicological effects, and are presented and discussed very extensively. Module 5 on the other hand, contains the raw data of the clinical study reports on the efficacy of the drug in length, with a particular focus on the benefit-risk aspect of the drug.

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## Drug Master File

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### Background

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these.

A DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application.

This guideline does not impose mandatory requirements (21 CFR 10.90(b)). It does, however, offer guidance on acceptable approaches to meeting regulatory requirements. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable.

Drug Master Files are provided for in 21 CFR 314.420. This guideline is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. The guideline discusses types of DMF's, the information needed in each type, the format of submissions to a DMF, the administrative procedures governing review of DMF's, and the obligations of the DMF holder.

DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new DMF.

### Definitions

For the purposes of this guideline, the following definitions apply:

1. Agency means the Food and Drug Administration.
2. Agent or representative means any person who is appointed by a DMF holder to serve as the contact for the holder.
3. Applicant means any person who submits an application or abbreviated application or an amendment or supplement to them to obtain FDA approval of a new drug or an antibiotic drug and any other person who owns an approved application (21 CFR 314.3 (b)).

4. Drug product means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3 (b)).
5. Drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3 (b)).
6. Export application means an application submitted under section 802 of the Federal Food, Drug, and Cosmetic Act to export a drug that is not approved for marketing in the United States.
7. Holder means a person who owns a DMF.
8. Letter of authorization means a written statement by the holder or designated agent or representative permitting FDA to refer to information in the DMF in support of another person's submission.
9. Person includes individual, partnership, corporation, and association. (Section 201(e) of the Federal Food, Drug, and Cosmetic Act.)
10. Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization (21 CFR 312.3 (b)).

## **Types of drug master files**

There are five types of DMF's:

Type I- Manufacturing Site, Facilities, Operating Procedures, and Personnel

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

Type III- Packaging Material

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

Type V- FDA Accepted Reference Information

### **1. Type I**

Manufacturing Site, Facilities, Operating Procedures, and Personnel

A Type I DMF is recommended for a person outside of the United States to assist FDA in conducting onsite inspections of their manufacturing facilities. The DMF should describe the manufacturing site, equipment capabilities, and operational layout. A Type I DMF is normally not needed to describe domestic facilities, except in special cases, such as when a person is not registered and not routinely inspected.

The description of the site should include acreage, actual site address, and a map showing its location with respect to the nearest city. An aerial photograph and a diagram of the site may be helpful. A diagram of major production and processing areas is helpful for understanding the operational layout. Major equipment should be described in terms of capabilities, application, and location. Make and model would not normally be needed unless the equipment is new or unique. A diagram of major corporate organizational elements, with key manufacturing, quality control, and quality assurance positions highlighted, at both the manufacturing site and corporate headquarters, is also helpful.

## 2. Type II

Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product.

A Type II DMF should, in general, be limited to a single drug intermediate, drug substance, drug product, or type of material used in their preparation.

Drug Substance Intermediates, Drug Substances, and Material Used in Their Preparation Summarize all significant steps in the manufacturing and controls of the drug intermediate or substance. Detailed guidance on what should be included in a Type II DMF for drug substances and intermediates may be found in the following guidelines:

Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.

Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application.

### Drug Product

Manufacturing procedures and controls for finished dosage forms should ordinarily be submitted in an IND, NDA, ANDA, or Export Application. If this information cannot be submitted in an IND, NDA, ANDA, or Export Application, it should be submitted in a DMF. When a Type II DMF is submitted for a drug product, the applicant/sponsor should follow the guidance provided in the following guidelines:

Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application.

Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products

Guideline for Submitting Samples and Analytical Data for Methods Validation

## 3. Type III

Packaging Material: Each packaging material should be identified by the intended use, components, composition, and controls for its release. The names of the suppliers or fabricators of the components used in preparing the packaging material and the acceptance specifications should also be given. Data supporting the acceptability of the packaging material for its intended use should also be submitted as outlined in the “*Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics.*”

Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross reference to another document.

## 4. Type IV

Excipient, Colorant, Flavor, Essence, or Material Used in their preparation

Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods.

Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross reference to another document.

Usually, the official compendia and FDA regulations for color additives (21 CFR Parts 70 through 82), direct food additives (21 CFR Parts 170 through 173), indirect food additives (21 CFR Parts 174 through 178), and food substances (21 CFR Parts 181 through 186) may

be used as sources for release tests, specifications, and safety. Guidelines suggested for a Type II DMF may be helpful for preparing a Type IV DMF. The DMF should include any other supporting information and data that are not available by cross reference to another document.

## **5. Types V**

### **FDA Accepted Reference Information**

FDA discourages the use of Type V DMF's for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMF's. If any holder wishes to submit information and supporting data in a DMF that is not covered by Types I through IV, a holder must first submit a letter of intent to the Drug Master File Staff (for address, see D.5.a. of this section). FDA will then contact the holder to discuss the proposed submission.

Each DMF should contain only one type of information and all supporting data. See Section IV.C of the guideline for more detailed descriptions of the kind of information desired in each type. Supporting information and data in a DMF can be cross referenced to any other DMF.

### **Submissions to drug master files**

Each DMF submission should contain a transmittal letter, administrative information about the submission, and the specific information to be included in the DMF as described in this section.

The DMF must be in the English language. Whenever a submission contains information in another language, an accurate certified English translation must also be included.

Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

#### **A. Transmittal Letters**

The following should be included:

### **Original Submissions**

- a. Identification of submission: Original, the type of DMF as classified in Section III, and its subject.
- b. Identification of the applications, if known, that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document numbers.
- c. Signature of the holder or the authorized representative.
- d. Typewritten name and title of the signer.

### **Amendments**

- a. Identification of submission: Amendment, the DMF number, type of DMF, and the subject of the amendment.
- b. A description of the purpose of submission, e.g., update, revised formula, or revised process.
- c. Signature of the holder or the authorized representative.
- d. Typewritten name and title of the signer.

## **Administrative Information**

Administrative information should include the following:

### **Original Submissions**

- a. Names and addresses of the following:
  - (1) DMF holder.
  - (2) Corporate headquarters.
  - (3) Manufacturing/processing facility.
  - (4) Contact for FDA correspondence.
  - (5) Agent(s), if any.
- c. The specific responsibilities of each person listed in any of the categories in Section a.
- c. Statement of commitment.

A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

### **Amendments**

- a. Name of DMF holder.
- b. DMF number.
- c. Name and address for correspondence.
- d. Affected section and/or page numbers of the DMF.
- e. The name and address of each person whose IND, NDA, ANDA, DMF, or Export Application relies on the subject of the amendment for support.
- f. The number of each IND, NDA, ANDA, DMF, and Export Application that relies on the subject of the amendment for support, if known.
- g. Particular items within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known

## **Drug Master File Contents**

### **General Information and Suggestions**

#### **A. Environmental Assessment**

Type II, Type III, and Type IV DMF's should contain a commitment by the firm that its facilities will be operated in compliance with applicable environmental laws. If a completed environmental assessment is needed, see 21 CFR Part 25.

#### **B. Stability**

Stability study design, data, interpretation, and other information should be submitted, when applicable, as outlined in the "*Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.*"

### **Format, Assembly, and Delivery**

-An original and duplicate are to be submitted for all DMF submissions.

Drug Master File holders and their agents/representatives should retain a complete

reference copy that is identical to, and maintained in the same chronological order as, their submissions to FDA.

-The original and duplicate copies must be collated, fully assembled, and individually jacketed.

Each volume of a DMF should, in general, be no more than 2 inches thick. For multivolume submissions, number each volume. For example, for a 3-volume submission, the volumes would be numbered 1 of 3, 2 of 3, and 3 of 3.

U.S. standard paper size (8-1/2 by 11 inches) is preferred.

Paper length should not be less than 10 inches nor more than 12 inches. However, it may occasionally be necessary to use individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula, or manufacturing instructions. Those pages should be folded and mounted to allow the page to be opened for review without

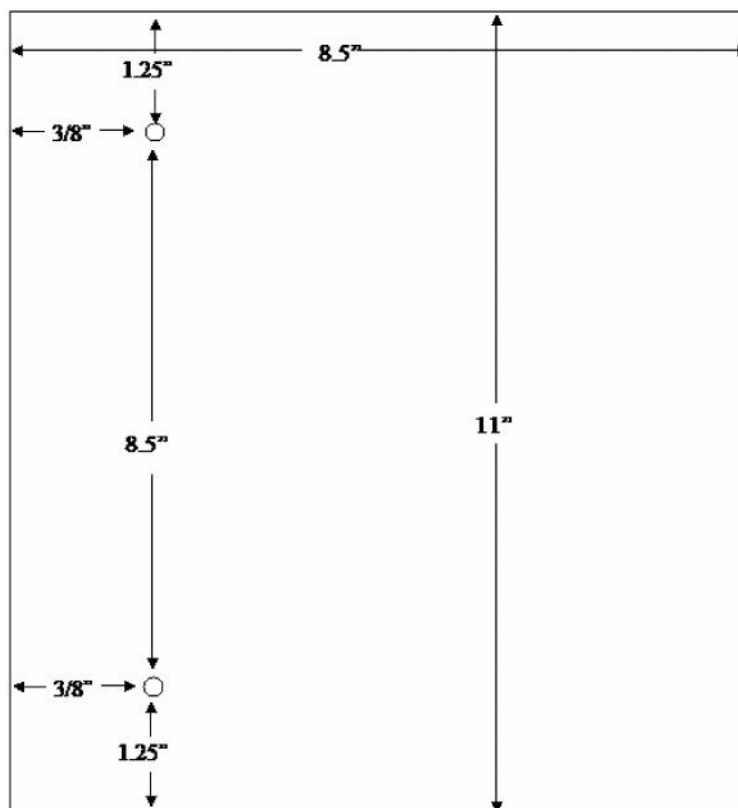


Figure 2- Format of Drug Master File

disassembling the jacket and refolded without damage when the volume is shelved.

The agency's system for filing DMF's provides for assembly on the left side of the page. The left margin should be at least three fourths of an inch to assure that text is not obscured in the fastened area. The right margin should be at least one half of an inch. The submitter should punch holes 8 1/2 inches apart in each page. See the page measurements shown in the following figure:

### **Delivery to FDA**

Drug Master File submissions and correspondence should be addressed as follows:

Drug Master File Staff

Food and Drug Administration  
5901-B Ammendale Rd.  
Beltsville, MD 20705-1266

Delivery charges to the above address must be prepaid.

## **Authorization to refer to a Drug Master File**

### **a. Letter of Authorization to FDA**

Before FDA can review DMF information in support of an application, the DMF holder must submit in duplicate to the DMF a letter of authorization permitting FDA to reference the DMF. If the holder cross references its own DMF, the holder should supply in a letter of authorization the information designated by items 3, 5, 6, 7, and 8 of this section. The holder does not need to send a transmittal letter with its letter of authorization.

The letter of authorization should include the following:

1. The date.
2. Name of DMF holder.
3. DMF number.
4. Name of person(s) authorized to incorporate information in the DMF by reference.
5. Specific product(s) covered by the DMF.
6. Submission date(s) of 5, above.
7. Section numbers and/or page numbers to be referenced.
8. Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it.
9. Signature of authorizing official.
10. Typed name and title of official authorizing reference to the DMF.

### **b. Copy to Applicant, Sponsor, or Other Holder**

The holder should also send a copy of the letter of authorization to the affected applicant, sponsor, or other holder who is authorized to incorporate by reference the specific information contained in the DMF. The applicant, sponsor, or other holder referencing a DMF is required to include a copy of the DMF holder's letter of authorization in the application.

## **Processing and Reviewing Policies**

### **a. Policies Related to Processing Drug Master Files**

Public availability of the information and data in a DMF is determined under 21 CFR Part 20, 21 CFR 314.420(e), and 21 CFR 314.430.

An original DMF submission will be examined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number.

If the submission is administratively incomplete or inadequate, it will be returned to the submitter with a letter of explanation from the Drug Master File Staff, and it will not be assigned a DMF number.

## **b. Drug Master File Review**

A DMF is never approved Or disapproved. The agency will review information in a DMF only when an IND sponsor, an applicant for an NDA, ANDA, or Export Application, or another DMF holder incorporates material in the DMF by reference. As noted, the incorporation by reference must be accompanied by a copy of the DMF holder's letter of authorization.

If FDA reviewers find deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. At the same time, FDA will notify the person who relies on the information in the deficient DMF that additional information is needed in the supporting DMF. The general subject of the deficiency is identified, but details of the deficiency are disclosed only to the DMF holder. When the holder submits the requested information to the DMF in response to the agency's deficiency letter, the holder should also send a copy of the accompanying transmittal letter to the affected persons relying on the DMF and to the FDA reviewing division that identified the deficiencies. The transmittal letter will provide notice that the deficiencies have been addressed.

### **Holder obligations**

Any change or addition, including a change in authorization related to specific customers, should be submitted in duplicate and adequately cross referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.

### **Notice Required for Changes to a Drug Master File**

A holder must notify each affected applicant or sponsor who has referenced its DMF of any pertinent change in the DMF (21 CFR 314.420(c)). Notice should be provided well before making the change in order to permit the sponsor/applicant to supplement or amend any affected application(s) as needed.

### **Listing of Persons Authorized to Refer to a Drug Master File**

A DMF is required to contain a complete list of persons authorized to incorporate information in the DMF by reference [21 CFR 314.420(d)]. The holder should update the list in the annual update. The updated list should contain the holder's name, DMF number, and the date of the update. The update should identify by name (or code) the information that each person is authorized to incorporate and give the location of that information by date, volume, and page number.

Any person whose authorization has been withdrawn during the previous year should be identified under a suitable caption.

If the list is unchanged on the anniversary date, the DMF holder should also submit a statement that the list is current.

### **Annual Update**

The holder should provide an annual report on the anniversary date of the original submission. This report should contain the required list as described in B.1., and should also identify all changes and additional information incorporated into the DMF since the previous annual report on the subject matter of the DMF. If the subject matter of the DMF is unchanged, the DMF holder should provide a statement that the subject matter of the DMF is current.



Failure to update or to assure FDA annually that previously submitted material and lists in the DMF remain current can cause delays in FDA review of a pending IND, NDA, ANDA, Export Application, or any amendment or supplement to such application; and FDA can initiate procedures for closure of the DMF (see Section IX).

### **Appointment of an Agent**

When an agent is appointed, the holder should submit a signed letter of appointment to the DMF giving the agent's name, address, and scope of responsibility (administrative and/or scientific). Domestic DMF holders do not need to appoint an agent or representative, although foreign DMF holders are encouraged to engage a U.S. agent.

### **Transfer of Ownership**

To transfer ownership of a DMF to another party, the holder should so notify FDA and authorized persons in writing. The letter should include the following:

- ❖ Name of transferee
- ❖ Address of transferee
- ❖ Name of responsible official of transferee
- ❖ Effective date of transfer
- ❖ Signature of the transferring official
- ❖ Typewritten name and title of the transferring official.

The new holder should submit a letter of acceptance of the transfer and an update of the information contained in the DMF, where appropriate. Any change relating to the new ownership (e.g., plant location and methods) should be included.

### **Major reorganization of a drug master file**

A holder who plans a major reorganization of a DMF is encouraged to submit a detailed plan of the proposed changes and request its review by the Drug Master File Staff. The staff should be given sufficient time to comment and provide suggestions before a major reorganization is undertaken.

### **Closure of a drug master file**

A holder who wishes to close a DMF should submit a request to the Drug Master File Staff stating the reason for the closure. See Section IV.D.5.a for the address.

The request should include a statement that the holder's obligations as detailed in Section VII have been fulfilled.

The Agency may close a DMF that does not contain an annual update of persons authorized to incorporate information in the DMF by reference and a list of changes made since the previous annual report. The holder will be notified of FDA's intent to close the DMF.

# Electronic Common Technical 163 Document (eCTD)

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## Background

eCTD (electronic Common Technical Document) is a standard format of submitting Regulatory information (such as applications, supplements, and reports) to the concerned Health Authorities (HAs). It provides a harmonized solution to implement the Common Technical Document (CTD) electronically. An eCTD consists of individual documents in PDF format which are arranged in a hierarchical form as per the CTD structure. It also has an XML backbone which cross-links required documents and provides information regarding the submission. The purpose of introducing eCTD was to reduce the burden on the reviewers of the HAs. It also simplifies the process of submission as all the Regulatory authorities use it as a standard format.

## There are total five modules in eCTD

1. Region-specific information
2. Summary documents
3. Information related to quality
4. Non-clinical study reports
5. Clinical study reports (CSRs)

## eCTD submissions are accepted for the following applications

- ❖ Investigational New Drug (INDs)
- ❖ New Drug Applications (NDAs)
- ❖ Abbreviated New Drug Applications (ANDAs)
- ❖ Biologics License Applications (BLAs)
- ❖ All the applications following the submission of the above-stated applications
- ❖ All the Master Files (MFs) which are part of any above-mentioned applications
- ❖ Major countries, such as the US, Europe, Australia, Canada, South Africa, Thailand, and Japan, are using eCTD as a standard format for submissions of documents because of numerous advantages that it offers over the traditional submission method. Some of which are:
  - ❖ Allows agencies to upload sequences automatically with the help of XML backbone
  - ❖ Reviewers can refer information easily with the help of hyperlinks
  - ❖ No need to scan, copy or store paper documents
  - ❖ Changes and updates made to the dossiers can be easily identified
  - ❖ Easy product lifecycle tracking
  - ❖ Simultaneous accessibility of documents is possible
  - ❖ eCTD is already included in global submission strategies of companies, worldwide. To stay ahead in the competition, companies are required to stay up-to-date with the eCTD requirements. Are your submissions eCTD compliant? Reach to Freyr at [sales@freyrsolutions.com](mailto:sales@freyrsolutions.com) to know more about eCTD submissions.

# **The Asian common technical dossier (actd) for the registration of pharmaceuticals for human use**

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## **Organization of the dossier**

This ASEAN Common Technical Dossier (ACTD) is a guideline of the agreed upon common format for the preparation of a well-structured Common Technical Dossier (CTD) application that will be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals and biologics for human use. Although the current ASEAN Common Technical Requirements (ACTR) has not included specific requirements for bio-similar products, the ACTD format is also applicable for bio-similar products. This guideline describes a CTD format that will significantly reduce the time and resources needed to compile applications for registration and in the future, will ease the preparation of electronic documental submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.

This guideline merely demonstrates an appropriate write-up format for acquired data. However, applicants can modify, if needed, to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results upon pharmaceutical registration.

Throughout the ACTD, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on either A4 or 8.5" x 11" paper. The left-hand margin should be sufficiently large that information is not obscured by the method of binding.

Font and size, (Times New Roman, 12-point font), for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Every page should be numbered, with the first page of each part designated as page 1. For a paper, Common Technical Acronyms and abbreviations should be defined the first time they are used in each part. References should be cited in accordance with the 1979 Vancouver Declaration on Uniform requirements for Manuscripts Submitted to Biomedical Journals.

The Common Technical Document is organized into four parts as follows:

### **Part I**

#### **Table of Contents, Administrative Data and Product Information**

Part I contains initially the overall Table of Contents of the whole ACTD to provide basically the information that could be looked through respectively. Secondly, the next content is the Administrative Data where required specific documentation in detail is put together such as application forms, label, and package insert etc. The last section of this part is Product Information where necessary information includes prescribed information, mode of action, side effects etc. A general introduction to the pharmaceutical, including its pharmacologic class and mode of action should be included. Part II. Quality Document

Part I contain Table of Content Administrative Information and Prescribing Information

Section A: Introduction

Section B: Overall ASEAN Common Technical Dossier Table of Contents

Section C: Documents required for registration (for example, application forms,

labelling, Product Data Sheet, prescribing information)

## **Part II**

### **Quality Document**

It should provide the Quality Overall Summary followed by the Body of Data. The quality control document should be described in detail as much as possible.

Part II contain three sections

Section A: Table of Contents

Section B: Quality Overall Summary

Section C: Body of Data

## **Part III**

### **Non-clinical Document**

Part III should provide the Nonclinical Overview, followed by the Nonclinical Written Summaries and the Nonclinical Tabulated Summaries. The documentation of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries. Therefore, the authority who requires specific Study Reports should ask for the necessary documents.

The word “Nonclinical” replaces “Pre-clinical”.

Part III contain four sections

Section A: Table of Contents

Section B: Nonclinical Overview

Section C: Nonclinical Written and Tabulated Summaries

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Section D: Nonclinical Study Reports

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

## **Part IV**

### **Clinical Document**

Part IV should provide the Clinical Overview and the Clinical Summary. The documentation of this part is not required for Generic Products, Minor Variation Products and some Major Variation Products. For ASEAN member countries, the Study Reports of this part may not be required for NCE, Biological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in

Reference Countries. Therefore, the authority who requires specific Study Reports should ask for the necessary documents.

The overall organisation of the Common Technical Dossier is presented on the following in Parts:

Section A: Table of Contents

Section B: Clinical Overview

Section C: Clinical Summary

1. Summary of Bio-pharmaceutics and Associated Analytical Methods
2. Summary of Clinical Pharmacology Studies
3. Summary of Clinical Efficacy
4. Summary of Clinical Safety
5. Synopses of Individual Studies

Section D: Tabular Listing of All Clinical Studies

Section E: Clinical Study Reports

Section F: List of Key Literature Reference

**CHAPTER 01**



**Clinical trials**

**Developing clinical trial protocols**

**Institutional Review Board / Independent  
Ethics committee –**

**formation and working procedures**

**Informed consent process and procedures**

**GCP obligations of Investigators**

**sponsors & Monitors**

**Managing and Monitoring clinical trials**

**Pharmacovigilance - safety monitoring in  
clinical trials**



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## Background

### Clinical trials developing clinical trial protocols

Writing a research proposal is probably one of the most challenging and difficult tasks as research are a new area for the majority of postgraduate and new researchers. The purpose of this article is to summarize the most important steps and necessary guidelines for producing a standard research protocol. Academic and administrative success of any project is usually determined by acquiring a grant for the related field of research. Hence, the quality of a protocol is primarily required to achieve success in this scientific competition.

Clinical research is conducted according to a plan (a protocol) or an action plan. The protocol demonstrates the guidelines for conducting the trial. It illustrates what will be made in the study by explaining each essential part of it and how it is carried out. It also describes the eligibility of the participants, the length of the study, the medications and the related tests.

A protocol is directed by a chief researcher. The health of the participants' will be regularly checked by members of the research team to ultimately ensure the study's safety and effectiveness.

#### Purpose of a Research Proposal

1. To raise the question to be researched and clarify its importance.
2. To collect existing knowledge and discuss the efforts of other researchers who have worked on the related questions (Literature view).
3. To formulate a hypothesis and objectives.
4. To clarify ethical considerations.
5. To suggest the methodology required for solving the question and achieving the objectives.

To discuss the requirements and limitations in achieving the objectives.

### Benefits of the Proposal to a Researcher

Allows the researcher to plan and review the project's steps. Serves as a guide throughout the research.

Forces time and budget estimates.

### Writing the protocol

Protocol writing allows the researcher to review and critically evaluate the published literature on the interested topic, plan and review the project steps and serves as a guide throughout the investigation. The proposal is an inevitable document that enables the researcher to monitor the progress of the project.

1. Title of the study
2. Administrative details
3. Project summary



4. Introduction to the research topic, background (Literature view)
6. Study objectives and/or questions. Statement of the problem.
7. Methodology: Study design, study population and methods of recruitment, variables list, sample size, methods of data collection, data collection tools, plan of analysis (analysis of data)
8. Project management: Work plan (Timeline-proposed schedule)
9. Strengths and limitations of the study
10. Issues for ethical review and approvals

### **Title of the study**

Title of proposal should be accurate, short, concise, and identify. **What** is the study about, **Who** are the targets, **Where** is the setting of the study and **when** it is launched, if applicable. It should make the main objective clear, convey the main purpose of the research and mention the target population. Carry maximum information about the topic in a few words; it is a good practice to keep the title to within 12-15 words. It should convey the idea about the area of research and what methods are going to be used in a compact, relevant, accurate, attractive, easy to understand, and informative way.

### **Administrative Details**

The following administrative details and a protocol content summary should follow the title page:

- a. Contents page list of relevant sections and sub-sections with corresponding page number.
- b. Signature page is signed by senior members of the research team and dated to confirm that the version concerned has been approved by them.
- c. Contact details for the research team members listing postal and e-mail addresses and telephone numbers for members of the research team.

### **Project summary**

The summary should be distinctive, concise and should sum up all the essentials of the protocol.

### **Introduction (Background)**

The background to the project should be concise and refer to the subject straight forwardly. In writing there view, attention should be drawn to the positives, negatives and limitations of the studies quoted. Introduction is concluded by explaining how the present study will benefit the community. The literature view should logically lead to the statement of the aims of the proposed project and end with the aims and objectives of the study. There view should include the most recent publications in the field and the topic of the research is selected only after completing the literature review and finding some gaps in it.

Introduction should briefly answer the importance of the topic, the gaps/lacunae in the literature, the purpose of the study and benefits for the society, from the study.

The research question should be described precisely and concisely. It is going to be the basis of designing the project. The definition of the problem should be clear so that a reader can straight forwardly recognize the real meaning of it.

## Study objectives (Aims)

The aims should be explicitly stated. These should be confined to the intention of the project and they should arise from the literature review. State the goal you need to achieve. The study aims or objectives emerge from the study questions/ hypothesis. They are answers to what are the possible responses to the research question or hypothesis under analysis and measure. Aims should be logical and coherent, feasible, concise, realistic, considering local conditions, phrased to clearly meet the purpose of the study and related to what the specific research is intended to accomplish. For example, to evaluate knowledge level regarding dental caries in primary school children in KSA (this is not detailed). The following should be added: Causes, treatment, preventive measures, etc.

The objectives should be (SMART objective): Specific, Measurable, Achievable, Relevant and Time based.

**a. Specific Aims:** Details of each objective that will finally lead to the achievement of the goal should be stated. Specific aims one by one should be listed concisely. It is good practice not to include too many aims in the study (2-5 best); too many objectives often lead to inaccurate and poorly defined results. Furthermore, aims should be achievable, realistic and specific with no general and ambiguous statements. They should be stated in action verbs that illustrate their purpose: i.e., “to determine, to compare, to verify, to calculate, to reduce, to describe, etc.

**b. Secondary objectives (optional):** These are referred to as ancillary and minor objectives that could be studied during the course of the study the formulation of objectives helps to focus the study and to avoid the collection of any unnecessary data and hence organize the study in clear and distinct stages.

**c. Hypothesis:** It is a statement based on sound scientific theory that recognizes the predicted or relation between two or additional assessable variables [11]. It is always developed in response to the purpose statement or to answer the research questions posed. Furthermore, hypothesis transforms research questions into a format amendable to testing or into a statement that predicts an expected outcome.

Types of hypothesis statements:

### Null hypothesis:

A null hypothesis is a statement that there is no actual relationship between variables ( $H_0$  or  $H_N$ ). It may be read as there is no difference between the groups to be compared and no relationship between the exposure and outcome under investigation.  $H_0$  states the contradictory of what the researchers expect. The final conclusion of the investigators will either keep a null hypothesis or reject it in support of an alternative hypothesis. It does not essentially mean that  $H_0$  is accurate when not rejecting it as there might not be an adequate proof against it.

### Alternative hypothesis

An alternative hypothesis is a statement that suggests a potential outcome that the researcher may expect ( $H_1$  or  $H_A$ ). This hypothesis is derived from previous studies where an evident difference between the groups to be compared is present. It is recognized only when a null hypothesis is rejected. Practically, hypotheses are stated in the null form, because they have their inferential statistics. Such hypotheses of no difference will be challenged by researchers and the result of the statistical testing gives the probability that the hypothesis

of no difference is true or false.

Aims should be logically linked and arranged according to the tested hypothesis statement.

Example:

Research question: Is there a difference in fluoride release between the Compomer and Glass- ionomer cement?

Null Hypothesis: There is no difference in fluoride release between the Compomer and Glass- ionomer cement.

Alternate Hypothesis: There is a difference in fluoride release between the Compomer and Glass-ionomer cement.

- ❖ The statement of the problem should provide a summary of exactly what the project is trying to achieve.
- ❖ What exactly do you want to study?
- ❖ Why is it worth studying?
- ❖ Does the proposed study have theoretical and or practical significance?
- ❖ Does it contribute to a new understanding of a phenomenon? (i.e., Does it address new or little-known material or does it treat familiar material in a new way or does it challenge an existing understanding or extend existing knowledge?)
- ❖ The justification of the research should be a convincing statement for the need to do it:
- ❖ How does the research relate to the priorities of the region and the country?
- ❖ What knowledge and information will be obtained?
- ❖ What is the ultimate purpose that the knowledge obtained from the study will serve?
- ❖ How will the results be disseminated? How will the results be used, and who will be the beneficiaries?

## **Methodology**

### **Methods and Materials**

It should describe in detail the 'Where', 'Who', 'How' the research will be conducted. It explains the study design and procedures and techniques used to achieve the proposed objectives. It defines the variables and demonstrates in detail how the variables will be measured. It details the proposed methodology for data gathering and processing.

Methodology composes an important part of the protocol. It assures that the hypothesis will be confirmed or rejected. It also refers to a thorough strategy to attain the objectives. The methods and materials are divided in to various subheadings:

#### **a. Study design (cross-sectional, case-control, intervention study, Rct, etc.)**

Proper explanation should be given as to why a particular design was chosen (on the basis of proposed objectives and availability of resources).

A study design is in fact the researcher's general plan to acquire the answer(s) to the hypothesis being tested. Here, strategies will be applied to develop balanced, correct, objective and meaningful information. It explains the methods that will be used to collect and analyze data. Proper selection of the study design is important to attain reliable and valid scientific results. Ethics, logistic concerns, economic feature sand scientific

thoroughness will determine the design of the study. Here, a chief concern is given to the legality of the results including potential bias mystifying issues. Randomized controlled clinical trial is the best to document a causal relationship between an exposure and its outcome [Table/Fig-4].

## **Purpose**

To determine frequency and burden of a disease

To identify the risk factors

To determine prognosis of a disease

To determine efficacy/effectiveness of a new treatment

To evaluate community programs

## **study Design**

- Cross-sectional survey (Prevalence)
- Cohort study (Incidence)
- Cohort study
- Case-Control study
- Cohort study
- Clinical trials
- Community intervention
- Evaluation

### **b. Study population (Study subjects)**

Where are you going to do the research and who is the study population (why doing research in this place and why selecting this population?).

It describes in detail about the study subjects, all aspects of the selection procedure and sample size calculation. Proper definition of eligibility, inclusion, exclusion and discontinuation criteria of the study subjects should be stated. Allocation of subjects to study arms should be explained and described in details bearing in mind the concealment and randomization process.

### **c. Sample size**

Sample size calculation is recommended for economical and ethical reasons [16-18]. The calculation of the sample size must be explained including the power of the sample. The sampling technique should be mentioned, e.g., randomization that will be used in order to obtain a representative sample for your target population. Each step involved in the recruitment of the study subjects should be described according to the selection criteria (inclusion and exclusion criteria). "Informed consent" should be mentioned (Permission granted in full knowledge of the possible consequences).

### **d. Proposed intervention**

Full description of proposed intervention should be given. Here, all the activities and actions should be recorded and thoroughly explained in their order of occurrence. When using drugs, both scientific and brand name should be mentioned followed by the name of the manufacturing company, city, and country. Drug route, dosage, frequency of administration, and total duration of treatment with the drug should be mentioned. When using apparatus its name should be given followed by the name of the manufacturer, city and country.

Involved personnel should precisely define:

- ❖ Who will be responsible for the interventions?

- ❖ What activities each personnel will perform and with what frequency and intensity?

### **e. Data collection methods, instruments used:**

Data collection tools are:

- ❖ Retrospective data (medical records)
- ❖ Questionnaires
- ❖ Interviews (Structured, Semi-Structured)
- ❖ Laboratory test (literature or personal knowledge should be referenced, if established test, or description should be provided in details, if not established)
- ❖ Clinical examinations
- ❖ Description of instruments, tools used for data collection, as well as the methods used to test the validity and reliability of the instrument should be provided.

### **f. Data Managements and Analysis Plan**

This section should be written following statistical advice from a statistician. The analysis plan and which statistical tests will be used to check the significance to the research question/hypothesis with appropriate references should be described. Names of variables that will be used in the analyses and the name of statistical analysis that will be performed to assess the outcome should be listed.

If computer programs are to be applied, it is important to mention the software used and its version.

### **Project Management**

Work plan-A work plan is an outline of activities of all the phase of the research to be carried out according to an anticipated time schedule. Proper time table for accomplishing each major step of the study should be defined. Assigning time frame to each step in the trial will be helpful in organizing the structure of the research trial. The personnel (investigators, assistants, laboratory technicians etc.) involved in the study or data collection should be properly trained.

#### **1. Strengths and limitations:**

It is important to mention the strengths or limitations of the study, i.e., what study can achieve or cannot achieve is important, so as to prevent wasteful allocation of resources.

#### **2. ethical considerations (issues for ethical Review and Approvals)**

It should indicate whether the procedures to be followed are in accord with the Declaration of Helsinki. In any case, study should not start unless approval from ethics committee is received.

The following points should be explained:

- The benefits and risks for the subjects involved. The physical, social and psychological implications of the research.
- Details of the information to be given to the study patients including alternative treatments/approaches.
- Information should be provided on the free informed consent of the participants. Information form should contain: Justification for research, outline of study, risks, confidentiality, and voluntary participation should be told patients about the freedom

to withdraw from the study whenever they wish to. Confidentiality indicates show the personal information obtained from the patient will be kept secret (Data safety).

### **3. Operational Planning and Budgeting (Budget summary)**

Outline the budget requirement showing head wise expenditure for the study-man power, transportation, instruments, laboratory tests and cost of the drug. Budget estimate is to be attached in the annexure. All costs including personnel, consumables, equipment, supplies, communication and funds for patients and data processing are all included in the budget. Each item should be justified

## **Institutional Review Board / Independent Ethics committee (IRB/IEC)**

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### **Formation and working procedures**

Institutional Review Board/Independent Ethics Committee (IRB/IEC) • IRB/IEC serves as an independent body that reviews, evaluates, approves and decides on the scientific and ethical aspects of the clinical trial protocol as well as the benefits and risks to the study participants • Main purpose of IRB/IEC is to protect the rights, safety, and well-being of the subjects who participate in a trial

### **Composition of IRB/IEC**

- ❖ Consists of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trials
- ❖ Includes at least five members, of which at least one member whose primary area of interest is nonscientific, and at least one member who is independent of the institution/ trial site

### **Responsibilities of IRB/IEC**

- ❖ Safeguard the rights, safety, and well-being of all trial subjects
- ❖ Reviews a proposed clinical trial within a reasonable time and document its views in writing
- ❖ Conducts continuing review of each ongoing trial at least once per year
- ❖ Ensures that information regarding payment to subjects (including the methods, amounts, schedule of payment) is set forth in the written informed consent form and any other written information is provided to the subjects

### **Procedures of IRB/IEC**

- ❖ Determines its composition and authority under which it is established
- ❖ Schedules, notifies its members of, and conducts its meetings
- ❖ Conducts initial and continuing review of trials
- ❖ Specifies that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial
- ❖ Specifies the information that the investigator should promptly report to the IRB/IEC (like deviations from the protocol, adverse drug reactions etc.)

## Maintenance of records of IRB/IEC

- ❖ IRB/IEC retains all relevant records (e.g., written procedures, lists of occupations/affiliations of members, submitted documents, minutes of meetings, etc.) for a period of at least 3 years after completion of the trial and makes them available upon request from the regulatory authority(is)
- ❖ IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists

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## Informed consent process and procedures

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### Introduction

Informed consent - the process of communication between a patient or research subject and a physician or researcher that results in the explicit agreement to undergo a specific medical intervention - is an ethical concept based on the principle that all patients and research subjects should understand and agree to the potential consequences of the clinical care they receive. Regulations that govern the attainment of informed consent for treatment and research are crucial to ensuring that medical care and research are conducted in an ethical manner and with the utmost respect for individual preferences and dignity. These regulations, however, often require - or are perceived to require - that informed consent documents and related materials contain language that is beyond the comprehension level of most patients and study participants

### The Informed Consent Process

The informed consent process is central to the ethical conduct of research. It is an ongoing conversation between the human research subject and the researchers that begins before consent is given and continues until the end of the subject's involvement in the research (see consent process diagram, below). There are various tools for the investigator to use to optimize this conversation, but the most important feature of informed consent is the investigator commitment to the process.

Goals of the informed consent process

- ❖ Give the subject **information** about the research
- ❖ Make sure the subject has **time** to consider all options
- ❖ Answer all of the subject's **questions** before the decision is made
- ❖ Make sure that all information is **understood** by the subject
- ❖ Obtain the subject's voluntary informed **consent** to participate
- ❖ **Continue to inform** the subject throughout the research study
- ❖ **Continue to re-affirm subject consent** to participate throughout the research study

Tools an investigator might use to assist the informed consent process

- ❖ Consent Form - also called Informed Consent Form (ICF), Informed Consent Document (ICD) or Patient Consent Form(PCF)\*
- ❖ Pamphlets or other reading materials\*
- ❖ Internet information\*

- ❖ Instruction sheets\*
- ❖ Audio-visual presentations\*
- ❖ Charts or diagrams\*
- ❖ Discussions
- ❖ Consultation with others

\*These items require IRB review before use.

### **Investigator responsibilities in regard to informed consent**

- ❖ Obtain consent before initiating study-specific procedures.
- ❖ Provide a **quiet, comfortable, and private setting** for the informed consent process whenever possible.
- ❖ **Explain** the consent process to the subject.
- ❖ Make sure the subject has **time to consider** all options; allow subject to take the form home before signing (whenever possible).
- ❖ Consider the **subject's reading abilities**. Check to make sure WIRB has not disallowed subjects unable to read. If enrollment of limited or non-readers is allowed, involve an impartial witness in the informed consent process.
- ❖ Answer all questions.
- ❖ To the extent possible, make sure the subject **understands enough information** about the research study to give informed consent.
- ❖ To the extent possible, make sure the subject can consent **free from coercion or other undue influence**.
- ❖ Since the informed consent process continues throughout the subject's participation in the study, **consent should be informally verified on a continuing basis**.
- ❖ **Significant new information** must be given to the subject, and continuing consent documented in some way; for example, new risk information presented to the subject in an addendum to be signed by subjects who agree to continue to participate.

### **Issues to consider during the consent process**

- ❖ Was the subject alert and, in your opinion, able to read and understand the language in the consent form?
- ❖ If the subject was unable to read the consent form, and limited or non-readers were allowed to participate, did you have an impartial witness present for the entire process? (An impartial witness is someone with adequate reading ability who is independent of the trial, who cannot be unfairly influenced by people involved in the trial, who attends the informed consent process while the consent form is being read to the subject, who reads the informed consent form and any other written information supplied to the subject, and who is willing to attest to this by signing the consent form).
- ❖ If the subject is not fluent in English, was an approved translation of the consent form provided in the primary language of the subject? Was there also a bilingual translator present to assist with the informed consent process? Note: a translator alone is not considered adequate.
- ❖ Was the subject under any pressure (for example, family pressure, lack of medical



insurance) to participate in the research? Was this discussed?

- ❖ Did the subject take time to carefully read the consent form, or read it along with you?
- ❖ Were the risks as set forth in the consent form carefully explained to the subject?
- ❖ Are there any other risks or concerns not stated in the consent form and were these explained to the subject?
- ❖ Was the subject asked if he or she had any questions about the study?
- ❖ Did the subject have any questions or concerns?
- ❖ Were the subject's questions answered?
- ❖ Was the subject satisfied with the answer(s) they were provided?
- ❖ Did the person conducting the consent discussion check for subject understanding by asking some basic questions about the research? Did the responses reflect adequate understanding?
- ❖ Did the subject express a clear decision to proceed with the study?
- ❖ Was the consent form signed by the person who conducted the informed consent discussion?
- ❖ Was the consent form signed by a witness (if required)?
- ❖ Was the consent form signed by the Principal Investigator (if required)?
- ❖ If a Legally Authorized Representative is allowed to sign for the subject
- ❖ subject's understanding and assent considered and addressed?

### **Consent by Legally Authorized Representatives**

The laws regulating who can consent for adults who lack the capacity to consent for themselves are defined at the state level and vary from state to state. Persons who can consent for adults who lack the capacity to personally provide informed consent are known as Legally Authorized Representatives (LARs). See 45 CFR 46.102(c) and 21 CFR 50.3(1). Such trials, unless an exception is justified, should be conducted in individuals having a disease or condition for which the investigational product is intended.

WIRB's initial review submission forms solicit information about plans for use of LARs from investigators who plan to enroll adults who lack the capacity to consent for themselves. Sites should be able to explain how they determine which individuals meet.

the criteria for being a Legally Authorized Representative (LAR) under their state/provincial and local law. WIRB can provide a copy of the relevant statutes for your state upon request; however, advice from your legal counsel is strongly recommended. Sites should also be able to explain the process they use for verifying that an individual is qualified to serve as an LAR.

If the site's state/provincial/local laws regarding Legally Authorized Representatives are difficult to interpret, the sites may provide the Board with a letter from legal counsel which includes a statement such as the following: "The individuals who are authorized under state law to consent on behalf of a prospective subject to that subject's participation in the procedures involved in this research protocol are

Consent by Subjects Who Cannot Physically Sign the Consent Form (due to physical impairment)

WIRB does not require a Legally Authorized Representative to provide consent for subjects who are cognitively capable of consenting, but physically unable (for example, due to paralysis). In those cases, obtaining consent from the subject with the assistance of a witness is usually sufficient. WIRB can provide additional guidance for these situations upon request.

### **Waivers of Consent for non-FDA studies**

If you are requesting a waiver of consent and the research is not an FDA regulated study, then criteria from 45 CFR 46.116(d) must be met:

- ❖ The research involves no more than minimal risk to the subjects.
- ❖ The waiver or alteration will not adversely affect the rights and welfare of the subjects.
- ❖ The research could not practicably be carried out without the waiver or alteration.
- ❖ Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

### **Waivers of Consent for FDA studies**

For FDA regulated studies, waiver of consent must meet requirements of either 21 CFR (a) - (c) (waiver of consent for individual emergency use) or 21 CFR 50.24 (emergency research without consent), or FDA guidance issued 04-25-2006 for In Vitro Diagnostic Device Study Using Leftover Human Specimens That Are Not Individually Identifiable.

For individual emergency waivers of consent, prospective IRB approval is not always necessary if a patient's life can be saved. See the FAQ on [www.wirb.com](http://www.wirb.com) titled "What is the difference between "Emergency Use" and "Treatment Use," and how do I determine which situation I have?" for more information, or refer to 21 CFR 50.23 (a)-(c).

### **Waiver of Documentation of Consent**

A waiver of documentation of consent is a waiver of the requirement for a signature on a consent form. The regulations allow the Board to approve this type of waiver if:

- ❖ The research is of minimal risk and involves no procedures for which written consent is usually required; or
- ❖ The only record linking the subject and the research would be the consent document and the principal risk of the research is the risk of breach of confidentiality.

Subjects enrolling in a study under this type of waiver must be provided with the elements of consent required by the regulations and subjects must consent to participate.

The Board will need to review the information that is provided to subjects to obtain consent to ensure that the required elements of consent are included in the consent discussion. Investigators requesting a waiver of documentation of consent must submit a written statement or script of this information for the Board's review.

### **The Consent Form**

The primary informed consent tool that involves both the researcher and the IRB is the consent form. This document is used in all research for which there is no approved waiver of consent. Thus, most research will involve use of an IRB-approved consent form.

An approved consent form must comply with several regulatory requirements:

- ❖ The required elements (as defined by the regulations) must be appropriately included.

- ❖ The content of the consent form must be understandable to anon-scientist.
- ❖ No waiver of rights or other exculpatory wording may be present or appear to be present in the consent form.

Satisfying the above requirements presents a joint challenge to the IRB and the investigator. In order to obtain WIRB approval of a consent form, the investigator may opt to do one, or a combination, of the following:

- ❖ Submit a sponsor template consent form for review (for multi-center studies, the sponsor template has often already been submitted to WIRB and reviewed)
- ❖ Submit an investigator-written consent form for review
- ❖ Request WIRB write the consent form

### **Some general guidelines for writing consent form**

Consent templates and/or outlines are available from WIRB, as well as from some NIH groups such as NCI, and other sources. See Appendix 1 for a sample Consent Template. Consent templates provide a framework and structure upon which to build a consent form.

- ❖ Consent forms should be written in simple, non-technical language for readers of a seventh-grade reading level who may not have taken science courses in school.
- ❖ Use the term “subject” rather than “patient” (the term “participant” may be used in some behavioral research).
- ❖ Avoid statements that suggest any waiver of subject rights or release from liability of the investigator or sponsor.
- ❖ Avoid use of “I understand” or “you understand” language as this may imply a level of understanding that is not present, and may discourage questions,
- ❖ Write all of the consent form except the consent section in the second person (“you are asked to”) rather than first person or third person.
- ❖ The consent section should be written in first person (“I consent to...”).
- ❖ Avoid wording that is, or may seem to be, coercive or overly reassuring to a potential subject.
- ❖ Do not make claims of safety or efficacy for investigational articles or procedures.
- ❖ Try to avoid the use of the terms “treatment,” “therapy” or “therapeutic” (because these words may imply effectiveness).

### **Consent form elements**

The following is a list of the usual elements of a consent form (including elements required by 21 CFR § 50.25; 45 CFR § 46.116; E 6 GCP 4.8.10).

#### **Introductory Information and Purpose**

- ❖ Explain the research study and the expected duration of subject participation, and include the approximate number of subjects involved in the study.
- ❖ Reassure readers that it is appropriate to ask questions, and that they may take the form home for consideration (if appropriate for the given research).
- ❖ State clearly that the study is research.

- ❖ State the status of the test article based on the country where the research is being conducted; for example, in the U.S., drugs are “approved,” vaccines are “licensed,” and devices are “cleared” or “approved for marketing,” otherwise they should be designated as “investigational.”
- ❖ State the purpose(s) of the research; for example, drug protocols usually test for safety, tolerability and effectiveness.
- ❖ State why the person is being asked to participate in the study; for example, “You are being asked to participate in this study because you have been diagnosed with...”

### **Description of Study/Procedures**

- ❖ Describe the visits and procedures (in agreement with the protocol), indicating which procedures are experimental.
- ❖ Briefly describe the study’s design; for example, “This is a dose escalation study. As subjects participating in the study tolerate a specific dose level, the new subjects entering the study will be given a higher dose of the study drug.”
- ❖ Explain the method used for determining if subjects will receive study drug or placebo, the method for assigning them to a group, and explain the chance of assignment to each group in the study.
- ❖ State the number of visits.
- ❖ Explain the length of study participation.
- ❖ Explain what happens at the visits. It is not necessary to list the procedures visit- by-visit, as detailed descriptions can result in an unnecessarily long consent form.
- ❖ Outline any additional participation requirements such as contraception requirements or prohibited activities.

### **Risks and Discomforts**

- ❖ Describe any reasonably foreseeable risks and discomforts to the subject. Risks and discomforts must be stated in non-technical, layperson’s language. Provide the risks related to all drugs required by the protocol, including rescue medications, over-the-counter analgesics, and approved control group drugs.
- ❖ Include the possibility of allergic reactions and that serious allergic reactions can be life-threatening.
- ❖ Describe the risks and discomforts of invasive or unusual procedures, including protocol- required biopsies.
- ❖ Describe the risks and discomforts of blood draws, if subjects will have blood drawn.
- ❖ Include a statement explaining that there may be risks of participation and side effects which are still unknown.
- ❖ Whether known or unknown, explain the risks to women who are pregnant or who become pregnant during the study.
- ❖ Include a statement that unknown risks and discomforts are possible; if appropriate, include unknown risks to an embryo or fetus if a subject (or a subject’s partner) is or becomes pregnant.
- ❖ Where applicable, include the risk that the subject’s condition may worsen while they are in the study (whether assigned to active drug or placebo).

- ❖ If the study drug will be taken home and there is no childproof packaging or warning labeling, include a warning to keep it out of reach of children or others who may not be able to read or understand the label.

### **Expected Benefits**

- ❖ Describe any possible benefits to the subject or others; indicate that benefits are not guaranteed.
- ❖ If statements regarding direct benefits of participation are included, they should be qualified as “possible” or that they “may” occur.

Receipt of procedures and study items may be listed as benefits to the subject, but not in conjunction with their being “free” or at “reduced cost,” as these statements imply a form of payment and thus should not be categorized as “benefits.” The FDA Information Sheet “Guidance for Institutional Review Boards and Clinical Investigators” (1998) states, “Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive.” Forms of payment may be referenced elsewhere, but not listed as a benefit of participation.

### **Alternatives**

- ❖ Describe appropriate alternative treatments or procedures, if available.
- ❖ List several alternatives to participation if they exist; alternatives may include alternative drugs or therapy, palliative care, hospice care, etc.
- ❖ The consent form may say, “Your study doctor will discuss these with you.”
- ❖ The section on alternatives should include a brief summary of the risks and benefits of the alternatives.

### **Costs**

- ❖ Describe any known or anticipated costs to the subject. State who is responsible for the costs of the study-related items such as medications, procedures, device, visits, hospitalization and treatment for possible side effects.
- ❖ Indicate which procedures and items will be provided at no charge.
- ❖ If insurance will be billed for anything, include information about possible costs to the subject or their insurance. If anything is being billed to insurance, discuss what happens if the insurance does not pay.

### **Payment for Participation**

- ❖ Describe the planned prorated payment for participation, if any.
- ❖ Any money or other incentive of monetary value should be listed in this section rather than the benefit section.
- ❖ If subjects are to be paid, state specifically for which visits subjects will receive payment and when such payment will be made; for example, “payment will be made at the end of each study visit,” “payment will be made at the end of the last study visit” or “payment will be made within one month after the last study visit.” Be as specific as possible to minimize confusion. Consider whether any aspects of the total amount or the proration plan may be coercive or unduly persuasive (WIRB does not routinely allow more than half the total payment to be assigned to the last visit). The Board may require revision of the payment or payment schedule.

- ❖ Compensation for Injury
- ❖ Outline the plans for compensation and/or medical treatment for research-related injury or illness, including who will be responsible for the costs.
- ❖ Explain what will happen if the subject gets injured. Explain how they will get treatment.
- ❖ Clearly state who will pay for treatment if the subject is harmed.
- ❖ Address what will happen if the subject's insurance is billed for the treatment, but refuses to pay.

WIRB requires that the clinical trials agreement (CTA) between the sponsor and the investigator (or investigator's institution) and the approved consent form do not conflict with each other regarding the compensation for injury. For example, if your CTA indicates that expenses for treatment of research related injury will be paid, the consent form must state this as well. Before submitting a request for review of a new research project to WIRB, please consider what method you will use to ensure that no subjects are enrolled unless the CTA and the WIRB-approved consent form are in agreement. WIRB accepts a variety of plans, for example:

- ❖ The research is minimal risk research for which compensation for injury language in the consent form is not necessary.
- ❖ There is no CTA for the research.
- ❖ The research is funded by a government agency (such as NIH) that does not offer compensation for injury.
- ❖ Upon receipt of WIRB approval documents, the investigator will check the CTA against the WIRB-approved consent form and resolve any conflicts via a request for a consent form modification to WIRB and/or a modified CTA before enrolling subjects.
- ❖ The sponsor or CRO may agree to review the WIRB-approved consent document and resolve any conflicts via a request for a consent form modification to WIRB and/or a modified CTA before authorizing enrollment at this site. WIRB requires the name and signature of the sponsor or CRO representative, or written correspondence from the sponsor or CRO indicating who will take this responsibility.
- ❖ The PI's hospital, university or medical center has a contract with WIRB for IRB services, and it has an established process for ensuring that the compensation for injury language in the CTA and in the consent form do not conflict.
- ❖ The PI's hospital, university or medical center has an established process for ensuring that the compensation for injury language in the CTA and in the consent form do not conflict. (Submitters must provide a description of the process.)
- ❖ Sites may also submit plans that differ from any of the plans outlined above.

### **Questions to be ask**

Regulations require that a contact be provided for each of the following types of questions.

- ❖ Questions about the research.
- ❖ Questions about research-related injury or illness (the Board prefers a physician be listed as the contact for injury or illness) or study problems.
- ❖ Questions about their rights as research subjects (list WIRB and, if desired, a local or

institution IRB contact).

- ❖ Voluntary Participation/Withdrawal
- ❖ State that the subject's participation is voluntary and that a subject may withdraw at any time for any reason.
- ❖ State that the subject's decision not to participate or to withdraw from the research early will involve no penalty or loss of benefits to which the subject is otherwise entitled.
- ❖ State that the subject's participation may be ended by the study doctor or sponsor at any time for any reason without the subject's consent. Include any specific reasons cited in the protocol. General reasons may also be included. Please note: the FDA may stop the research, but will not stop the participation of an individual subject.
- ❖ Include information on any risks involved with withdrawing early; for example, the need to taper the study drug, obtain follow-up, be placed on standard medication, etc.
- ❖ Indicate that subjects who withdraw after the start of the study may be asked to return for a final visit and final study procedures, and must return the study drug.

## **Trial Registration**

A new rule for informed consent was announced in the Federal Register: January 4, 2011 (Volume 76, Number 2) Page 256-270. The compliance date is March 7, 2012 for clinical trials that are initiated on or after the compliance date. As of that date, the following statement must be included in consent forms for "applicable clinical trials" as defined in FDAAA, 42 U.S.C. 282(j)(1)(A), section 402(j)(1)(A) of the PHS Act, and any relevant regulation.

"A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Since this wording is only required for certain types of clinical trials, and only for those initiated on or after the compliance date, WIRB will not be automatically including the text in all existing and new consent forms. Individuals that wish to have the text in their consent forms must request it. As the compliance date nears, our submission forms will be revised to collect the information needed to include the text in consent forms when appropriate.

## **Other**

- ❖ Explain that significant new information that may be related to the subject's willingness to remain in the research will be provided to the subject.
- ❖ Identify the source of funding for the research.
- ❖ Disclose conflicts of interest (financial and otherwise).
- ❖ State that the subject will receive a copy of the signed and dated consent form.

## **Consent**

This section changes to first person for emphasis; for example, "I voluntarily agree..." or "I have..."

- ❖ Include a statement of the subject's consent to participate, as well as an authorization to release medical (or research, as appropriate) records to the parties in the HIPAA authorization (or confidentiality) section, if applicable; and a statement that the subject

is not giving up any legal rights by signing the consent form.

- ❖ Include a statement that the subject has read the information in the consent form or had it read to her/him (as appropriate); however, don't include statements which imply a level of comprehension, such as "I understand..."
- ❖ Include a statement that the subject's questions have been answered.
- ❖ Signatures and Dates
- ❖ Include appropriate signature and date lines for consent as applicable.
- ❖ Include a space for the person conducting the informed consent discussion to sign (required by ICH).
- ❖ Provide a line for the investigator to sign if desired by researcher or sponsor; however, this is not a WIRB requirement.

### **Pregnant Partner Consent**

Many protocols now include instructions for investigators to collect data on the outcome of pregnancies that occur in partners of male subjects. WIRB follows 45 CFR 46, which defines research as use of private, identifiable information for research purposes. Since investigators would be obtaining private information from the pregnant partner and infant, the partner would be a subject in the research. Investigators must obtain consent from the pregnant partner before any data collection can occur, and WIRB requires a consent form to be submitted for these subjects if a pregnancy occurs.

If plans for obtaining consent from the pregnant partner (or a request for a consent waiver) are not submitted at initial review, the Board may approve the research, but send a letter reminding the investigator and sponsor that pregnant partners and their infants cannot be followed-up until WIRB approves a consent plan for them. Please note that no action is necessary until such time as a pregnancy occurs.

A sample consent form template for obtaining consent from partners who become pregnant and for collecting data about their infants is available in Appendix 4 of this document and on the Download Forms page of [www.wirb.com](http://www.wirb.com). The template consent form cannot be used without WIRB approval.

## **GCP obligations of Investigators, sponsors & Monitors**

### **Investigator**

#### **Investigator's Qualifications and Agreements**

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The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.



The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

### **Adequate Resources**

The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

### **Addendum**

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

### **Medical Care of Trial Subjects**

A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for inter current illness(es) of which the investigator becomes aware.

It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

### **Communication with IRB/IEC**

Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent

form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

## **Compliance with Protocol**

The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) To the IRB/IEC for review and approval/favorable opinion,
- (b) To the sponsor for agreement and, if required,
- (c) To the regulatory authority(ies).

## **Investigational Product(s)**

Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

The investigational product(s) should be stored as specified by the sponsor (see 5.13.2

and 5.14.3) and in accordance with applicable regulatory requirement(s).

The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

### **Randomization Procedures and Unblinding**

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

### **Informed Consent of Trial Subjects**

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favorable opinion by the IRB/IEC.

The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not

to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- (a) That the trial involves research.
- (b) The purpose of the trial.
- (c) The trial treatment(s) and the probability for random assignment to each treatment.
- (d) The trial procedures to be followed, including all invasive procedures.
- (e) The subject's responsibilities.
- (f) Those aspects of the trial that is experimental.
- (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- (j) The compensation and/or treatment available to the subject in the event of trial-related injury.
- (k) The anticipated prorated payment, if any, to the subject for participating in the trial.
- (l) The anticipated expenses, if any, to the subject for participating in the trial.
- (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a

written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

- (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- (s) The expected duration of the subject's participation in the trial.
- (t) The approximate number of subjects involved in the trial.

Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- (a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
- (b) The foreseeable risks to the subjects are low.
- (c) The negative impact on the subject's well-being is minimized and low.
- (d) The trial is not prohibited by law.
- (e) The approval/favorable opinion of the IRB/IEC are expressly sought on the inclusion of such subjects, and the written approval/ favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When

prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

## **Records and Reports Addendum**

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

## **Progress Reports**

The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

## **Safety Reporting**

All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

## **Premature Termination or Suspension of a Trial**

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

## **Final Report(s) by Investigator**

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

## **Sponsor**

## **Addendum**

## **Quality Management**

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

### **Critical Process and Data Identification**

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

### **Risk Identification**

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

### **Risk Evaluation**

The sponsor should evaluate the identified risks, against existing risk controls by considering:

- (a) The likelihood of errors occurring.
- (b) The extent to which such errors would be detectable.
- (c) The impact of such errors on human subject protection and reliability of trial results.

### **Risk Control**

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

### **Risk Communication**

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by



such activities, to facilitate risk review and continual improvement during clinical trial execution.

### **Risk Review**

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

### **Risk Reporting**

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

### **Quality Assurance and Quality Control**

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

### **Contract Research Organization (CRO)**

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

### **Addendum**

The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

### **Medical Expertise**

The sponsor should designate appropriately qualified medical personnel who will be

readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

### **Trial Design**

The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

### **Trial Management, Data Handling, and Record Keeping**

The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

#### **ADDENDUM**

- b) The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.
- c) Maintains SOPs for using these systems.

#### **Addendum**

- d) The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.
- e) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
- f) Maintain a security system that prevents unauthorized access to the data.
- g) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

- h) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

## **Addendum**

Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

## **Investigator Selection**

The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection is the sponsor's responsibility.

Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

The sponsor should obtain the investigators/institution's agreement:

- a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC (see 4.5.1);
- b) to comply with procedures for data recording/reporting;
- c) to permit monitoring, auditing and inspection (see 4.1.4) and
- d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).
- e) The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

### **Allocation of Responsibilities**

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

### **Compensation to Subjects and Investigators**

If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

### **Financing**

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

### **Notification/Submission to Regulatory Authority(ies)**

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

### **Confirmation of Review by IRB/IEC**

The sponsor should obtain from the investigator/institution:

- a) The name and address of the investigator's/institution's IRB/IEC.
- b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.
- c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents

that the IRB/IEC may have requested.

If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC re-approvals/re-evaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

### **Information on Investigational Product(s)**

When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

### **Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)**

The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bio-availability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

### **Supplying and Handling Investigational Product(s)**

The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

The sponsor should:

- a) Ensure timely delivery of investigational product(s) to the investigator(s).
- b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).
- c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaims).
- d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

The sponsor should:

- a) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples
- b) Should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

## **Record Access**

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

The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

## **Safety Information**

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

## **Adverse Drug Reaction Reporting**

The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

## **Monitor Monitoring**

### **Purpose**

The purposes of trial monitoring are to verify that:

- (a) The rights and well-being of human subjects are protected.
- (b) The reported trial data are accurate, complete, and verifiable from source documents.
- (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

## **Selection and Qualifications of Monitors**

- (a) Monitors should be appointed by the sponsor.
- (b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.
- (c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

**Extent and Nature of Monitoring** The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general, there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

## **Addendum**

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

- a) Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
- b) Examine data trends such as the range, consistency, and variability of data within and across sites.
- c) Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
- d) Analyze site characteristics and performance metrics.
- e) Select sites and/or processes for targeted on-site monitoring.

### **Monitor's Responsibilities.**

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- a. Acting as the main line of communication between the sponsor and the investigator.
- b. Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- c. Verifying, for the investigational product(s):
  - i. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
  - ii. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
  - iii. Those subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
  - iv. That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
  - v. That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
- d. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
- e. Verifying that written informed consent was obtained before each subject's participation in the trial
- f. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s)
- g. Ensuring that the investigator and the investigator's trial staff are adequately informed



about the trial.

- h. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
- i. Verifying that the investigator is enrolling only eligible subjects.
- j. Reporting the subject recruitment rate.
- k. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- l. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- m. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
  - i. The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
  - ii. Any dose and/or therapy modifications are well documented for each of the trial subjects.
  - iii. Adverse events, concomitant medications and inter current illnesses are reported in accordance with the protocol on the CRFs.
  - iv. Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
  - v. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.
- n. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
- o. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).
- p. Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).
- q. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

## **Monitoring Procedures**

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

## **Monitoring Report**

- a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

- b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.
- c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.
- d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

### **Addendum**

- a) Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

### **Addendum**

#### **Monitoring Plan**

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

#### **Audit**

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

#### **Purpose**

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

##### Selection and Qualification of Auditors

- a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.
- b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

#### **Auditing Procedures**

- a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.
- b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects

in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

- c) The observations and findings of the auditor(s) should be documented.
- d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.
- e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

## **Noncompliance**

Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

## **Addendum**

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

If the monitoring and/or auditing identify serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

## **Premature Termination or Suspension of a Trial**

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

## **Clinical Trial/Study Reports**

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

## **Multicenter Trials**

For multicenter trials, the sponsor should ensure that: All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC. The CRFs are designed to capture the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that is

designed to capture the additional data. The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial. All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs. Communication between investigators is facilitated

## **Managing and monitoring clinical trials**

### **Background**

Pharmacovigilance is majorly known as drug safety. It is a main integral part of clinical research. Throughout the product life cycle clinical trials safety and post marketing pharmacovigilance plays a critical role [1-3]. The word pharmacovigilance is derived from two words one Pharmakon is a Greek word which means “drug” and another vigilare is a Latin word which means to keep awake or to keep watch.” Pharmacovigilance is “defined as the pharmacological science relating to the detection, understanding, assessment and prevention of adverse effects, particularly long term and short-term adverse effects of medicines”.

According to WHO Pharmacovigilance (PV) is the pharmacological science relating to the detection, evaluation, understanding and prevention of adverse effects, especially long term and short-term side effects of medicines.

### **Aims of pharmacovigilance**

- ❖ To improve patient care & safety
- ❖ To contribute to assessment of benefit, harm & effectiveness of medicine
- ❖ To Identify previously unrecognized adverse effects of the drugs
- ❖ To Promote rational & safe use of medicine
- ❖ To Promote education & clinical training
- ❖ To Identify patient related risk factors of ADR such as dose, age, gender
- ❖ Any response to a drug which is unintended, occurs at particular doses
- ❖ To diagnose or therapy of disease, or for the modification, of physiological function.

Pharmacovigilance helps in removal of approved and licensed products from the market because of clinical toxicity, which is caused by adverse drug reactions in the body. Below is a short note on adverse drug reactions.

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## **Pharmacovigilance - safety monitoring in clinical trials**

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Clinical monitoring is the oversight and administrative efforts that monitor a participant’s health and efficacy of the treatment during a clinical trial. Both independent and government-run grant-funding agencies, such as the National Institutes of Health (NIH)<sup>[1]</sup> and the World Health Organization (WHO), require data and safety monitoring protocols for Phase I and II clinical trials conforming to their standards

### **Safety monitoring**

Safety monitoring of a clinical trial is conducted by an independent physician with relevant expertise. This is accomplished by review of adverse event, immediately after they occur, with timely follow-up through resolution.<sup>[4]</sup>

Responsibility for data and safety monitoring depends on the phase of the study and may be conducted by sponsor or Contract research organization (CRO) staff or contractor, and/or by the Principal clinical investigator/project manager conducting the study. Regardless of the method used, monitoring must be performed on a regular basis. Oversight of the monitoring activity is the responsibility of the sponsor.

### **Aspect of monitoring**

According to the U.S. Food and Drug Administration's Center of Drug Evaluation and Research, the top five deficiency categories for site inspections caught by clinical monitors as reported in the 2001 Report to the Nation<sup>[5]</sup> are:

- ❖ Failure to follow investigation protocol (the procedures and treatment subjects must undergo, as well as the schedule of assessments)
- ❖ Failure to keep adequate and accurate records
- ❖ Problems with the informed consent form
- ❖ Failure to report adverse events
- ❖ Failure to account for the disposition of study drugs

Therefore, the primary goal of clinical trial monitoring is to observe each trial site to ensure that the standardized operation procedures for the trial are being followed, reporting and managing any deviations from the investigation plan as they occur. Monitoring plans in the United States typically also require a clear protocol for reporting adverse/undesirable effects caused by the treatment to the institutional review board (IRB), the US Food & Drug Administration (FDA), and the institution funding the research.<sup>[3][6]</sup> The FDA itself maintains an Adverse Event Reporting System for such occurrences in clinical trials it oversees in the United States.

### **Function of clinical Monitor**

Clinical monitors execute the monitoring plan laid out by the sponsors and investigators of a clinical trial. Monitors may be referred to by many different titles, such as: Clinical Research Associate, "on-site" monitor, Clinical Research Monitor, Study Site Monitor and Quality Specialist. The number of clinical monitors depends on the scale and scope of the trial.

Almost all field monitoring requires regular visits to the site by the clinical research associate throughout the period of the study. On occasion, an extremely simple, low-risk study might be monitored almost exclusively by telephone except for the startup and closeout visits. Since the concept of "low risk" is subjective, this definition should be established in internal policies and procedures.

### **Complexity and Monitoring**

The level of scrutiny of monitoring varies across studies based on risks and nature of the trial.

Considerations that affect the design of monitoring plans usually include<sup>[6][3]</sup>:

- ❖ Complexity of the protocol (including toxicity, presence of special populations inside sample groups, amount of interaction needed, length of treatment, etc.)
- ❖ Risk of the treatment
- ❖ Disease being evaluated

- ❖ Number of study subjects enrolled at the site
- ❖ Number of treatment sites (such as number of clinics with access to and assigning the treatment)
- ❖ Site performance
- ❖ Sponsor monitoring standard operating protocols

Several of these factors depend on the phase of the clinical trial—for example, in some early Phase I studies of drugs whose effects on different individuals are unknown, the monitor may be required to be present during all or part of a subject's treatment, while Phase II investigations usually involve multiple investigation sites<sup>[2]</sup>.

The overall monitoring plan should remain fairly consistent, but the strategy for individual sites may change considerably during the course of the study depending on study conditions and site performance.

### **Adverse Drug Reactions**

ADR is a response to drug, which alters the normal physiological function of the body, factors which causes ADR includes mainly multiple drug therapy, age & gender.

They are mainly two types of ADR

**TYPE A:** These are common, predictable, dose dependent, they are seldom fatal

**TYPE B:** These are uncommon, unpredictable, dose independent; they involve relatively high rates of serious morbidity.

High index of ADRs are to be successfully diagnosed by clinicians, it is the high level of awareness about the drugs being used. Pharmacovigilance, unify all the information in all aspects of benefit-risk ratio of drugs in a population. Events that occur when a particular drug is administered are recorded in the patient's notes by drug monitoring then an adverse reaction of the drug and the activity of the drug being monitored; these studies aim to detect ADR of drugs

Reporting of ADRs after marketing must be actively encouraged and should involve all those concerned including doctors, pharmacists, nurses, patients and pharmaceutical companies. To develop and enhance this, a culture of learning about pharmacovigilance for health care students must be started in their early professional carrier. This will help healthcare professionals to understand and also create awareness by giving adequate information to patients at their initial phase of treatment about the potential benefits and risks of the therapy In the process of development of a new pharmaceutical drug, there are many stages they are preclinical trials, then clinical trials this includes four phases. In this the first three phase's helps in the determination of safety, efficacy and side effects of the developed drug product respectively, whereas in case of fourth phase post marketing studies are carried out for determining safety in patients. Thus, post marketing surveillance helps in uplifting the knowledge of pharmacovigilance.

### **Post marketing surveillance**

Pharmaceutical drug or medical device is monitored often after it has been released in to the market, Since drugs are approved based of clinical trials which involve relatively small number of people who do not have any other medical complications, post marketing surveillance play an important role to know the ADRs of drugs after they have released in to the market [60-67].

Approaches by

- spontaneous ADR reporting
- Prescription event monitoring
- Electronic health records
- Patient Registers

### **Spontaneous ADR Reporting**

It is necessary to report ADRs to Pharmacovigilance department by doctors, health care professionals, they are provided with forms where they can notify the suspected ADRs they detect, these forms are greatly available to health care professionals to encourage the reporting, it helps in spontaneous reporting for all the drugs, it is affordable method of detecting rare ADRs. This spontaneous reporting helps to identify many unexpected ADRs, it helps in withdrawal of many marketed drugs, and information being provided which guide safer use of the product.

ADRs which occurred by particular drugs should be analyzed and reported, Pharmaceutical manufacturers have to communicate with the doctors at the clinical level regarding the ADRs by

- ❖ Changing Medication formula if necessary
- ❖ Implementing new prescribing procedures
- ❖ Implementing new dispensing procedures
- ❖ Educating the professional staff
- ❖ Educating Patients

### **Prescription Event Monitoring**

It involves health professionals submitting all the clinical events reported by the patient to the prescribed new drug.

This method mainly focuses on studying the safety of new medications that are used by general practitioners in this method.

In this method patients being prescribed by drugs are monitored.

### **Electronic Health Records**

It is a computer stored collection of health information, about one person linked by a person identifier; it represents the basis for healthcare Information system development [86].

### **Patient Registers**

To bring together patient records, it is time consuming and less expensive

### **Pharmacovigilance programme of India (PVPI)**

It officially starts on 23rd November 2004 at New Delhi, is under the control of CDSCO (Central Drug Standard Control Organization), Directorate general of health services, Indian pharmacopeia commission (Ghaziabad). The program is conducting by NCC (National Coordinating Centre) to ensure that the benefits of use of medicine against the risks.

It was Launched by the MoHFW, Govt. of India in the year 2010 at AIIMS New Delhi

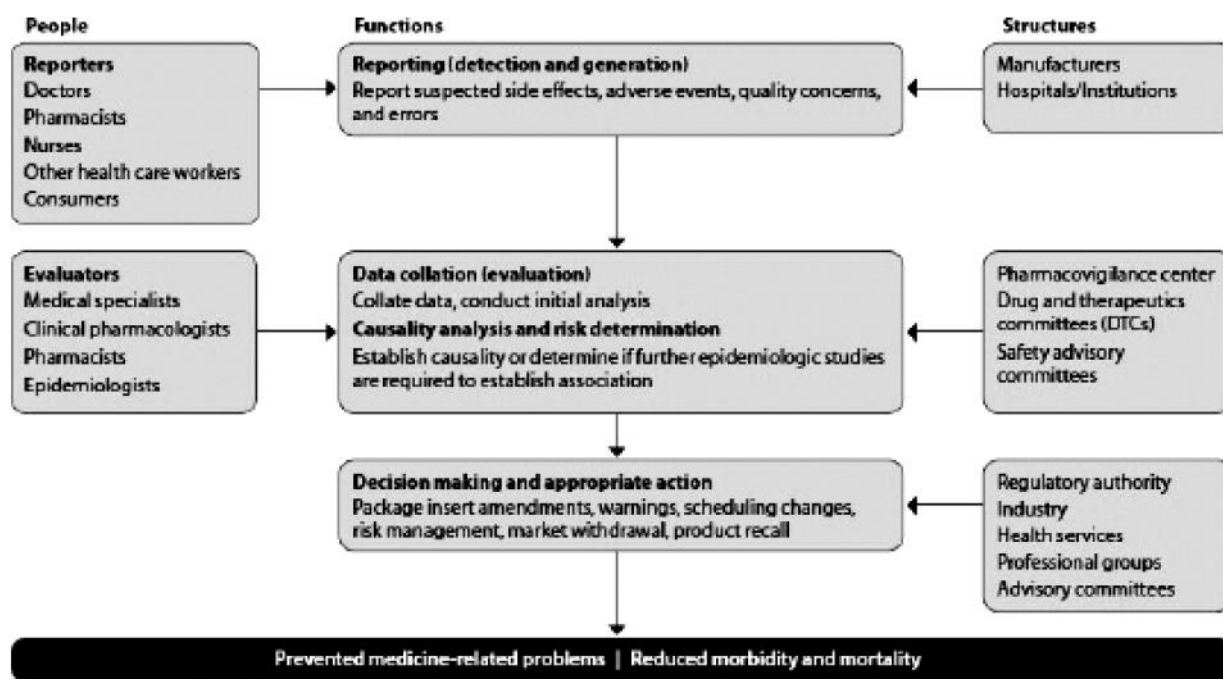


Figure 1: The Pharmacovigilance Framework

as National Coordinating Centre (NCC). ? The Programme transferred to IPC as NCC in April, 2011 by a Notification issued by the MoHFW, Govt. of India. ? IPC-PvPI became the NCC for Materiovigilance Programme of India (MvPI) from July, 2015 ? IPC, NCC-PvPI became a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes & Regulatory services from July, 2017

### Objectives:

- To monitor ADRs
- To create awareness among health care professionals about ADRs
- To monitor benefit-risk profile of medicines
- Support the CDSCO

### Pharmacovigilance in Acts & Rules

Pharmacy Council of India: Pharmacovigilance as one of the subjects in Pharmacy Under Graduate curriculum

Drugs & Cosmetic Act & Its rules 1945: establishment of Pharmacovigilance cell in the pharmaceutical industry is mandatory.

National Health Policy: Pharmacovigilance includes Prescription Audit inclusive of Antibiotic usage, Ministry of Health & Family Welfare, Government of India.





**CHAPTER 01**



**Regulatory Concepts**

**Basic terminology**

**Guidance**

**Guidelines**

**Regulations**

**Orange Book**

**Federal Register**

**Code of federal regulatory**

**Purple book**



**Investigational product-** New medicine developed by a manufacturer

**Phase III clinical study-**

Randomized study carried out by the manufacturer to assess the benefits and harms of an investigational product

**Active comparator (active treatment or active control)-** Medically effective treatment given as control condition in clinical studies

**Placebo-** Medically ineffectual treatment given as control condition in clinical studies

**Three-arm study-** Clinical study randomly allocating patients to one of the following three conditions: (1) investigational product; (2) active comparator; (3) placebo

**Two-arm head-to-head study (comparative trial)-**

Clinical study randomly allocating patients to one of the following two conditions:

- (1) Investigational product;
- (2) Active comparator

**Superiority to placebo-** Clinical study designed to demonstrate that the difference in terms of primary outcome between the investigational product and placebo is statistically significant in favor of the new medicine

**Superiority to an active comparator-** Clinical study designed to demonstrate that the difference in terms of primary outcome between the investigational product and an active comparator are statistically significant in favor of the new medicine

**Non-inferiority to an active Comparator-** Clinical study designed to demonstrate that the efficacy of an investigational product is not clinically inferior to an active comparator

**Efficacy in absolute terms-** An investigational product supported by evidence of superiority to placebo but not to an active comparator

**Added value-** An investigational product supported by evidence of superiority to an active comparator.

**Compulsory required**

According to EMA guidelines, some study designs are necessary to prove the efficacy of an investigational product for a given disorder, and therefore these studies must be conducted to obtain a marketing authorization.

**Recommended**

According to EMA guidelines, some study designs are methodologically appropriate to prove the efficacy of an investigational product for a given disorder, and therefore these studies are recommended to obtain a marketing authorization, although EMA recognizes that there may be alternative designs

## Acceptable

According to EMA guidelines, some study designs may be appropriate to prove the efficacy of an investigational product for a given disorder, and therefore these studies may be considered to obtain a marketing authorization, although EMA points out that there may be better alternative designs.

## Guidance, Guidelines, Regulations

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### Indian Regulations & Guidelines

#### CDSCO

**Central Drugs Standard Control Organization (CDSCO)**, Ministry of Health & Family Welfare, Government of India provides general information about drug regulatory requirements in India.

#### NPPA

**Drugs (Price Control) Order 1995** and other orders enforced by **National Pharmaceutical Pricing Authority (NPPA)**, Government of India. View the list of drugs under price control here.....

#### D & C Act, 1940

**The Drugs & Cosmetics Act, 1940** regulates the import, manufacture, distribution and sale of drugs in India.

#### Schedule M

**Schedule M** of the D&C Act specifies the general and specific requirements for factory premises and materials, plant and equipment and minimum recommended areas for basic installation for certain categories of drugs.

#### Schedule T

**Schedule T** of the D&C Act prescribes GMP specifications for manufacture of Ayurvedic, Siddha and Unani medicines.

#### Schedule Y

The clinical trials legislative requirements are guided by specifications of **Schedule Y** of the D&C Act.

#### GCP guidelines

**The Ministry of Health**, along with **Drugs Controller General of India (DCGI)** and **Indian Council for Medical Research (ICMR)** has come out with draft guidelines for research in human subjects. These **GCP guidelines** are essentially based on Declaration of Helsinki, WHO guidelines and ICH requirements for good clinical practice.

**The Pharmacy Act, 1948**

**The Pharmacy Act, 1948** is meant to regulate the profession of Pharmacy in India.

**The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954**

**The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954** provides to control the advertisements regarding drugs; it prohibits the advertising of remedies alleged to possess magic qualities.

**The Narcotic Drugs and Psychotropic Substances Act, 1985**

**The Narcotic Drugs and Psychotropic Substances Act, 1985** is an act concerned with control and regulation of operations relating to Narcotic Drugs and Psychotropic Substances.

**Links to important international guidelines and regulatory bodies:**

**WHO (Medicines)**

**WHO guidelines** on medicines policy, intellectual property rights, financing & supply management, quality & safety, selection & rational use of medicines, technical cooperation and traditional medicines.

**WHO sites**

**WHO guidelines** on all areas relevant to health of people all over.

**ICH**

**International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH)** guidelines defining quality, safety, efficacy & related aspects for developing and registering new medicinal products in Europe, Japan and the United States

**OECD**

**Organization for Economic Collaboration and Development** including 30 member countries covers economic and social issues in areas of health care.

**EMA**

**European Medicines Agency (EMA)**, a decentralized body of the European Union headquartered in London, prescribes guidelines for inspections and general reporting and all aspects of human & veterinary medicines in the European Union.

**US FDA**

Regulations, guidelines, notifications, news and communications from **US Food and Drug Administration**.

<b>TGA</b>	Specifications regulating medicines, medical devices, blood, tissues & chemicals, issued by <b>Therapeutic Goods Administration</b> , the Australian regulatory body.
<b>South Africa</b>	The department of Health, South Africa.
<b>WTO</b>	News, resources, documents and publications of the <b>World Trade Organization (WTO)</b> , the global international organization dealing with the rules of trade between nations.
<b>Codex Alimentarius</b>	Collection of international food standards and guidelines for processed, semi-processed and raw foods, adopted by the <b>Codex Alimentarius Commission under the Joint FAO / WHO Food Standards Programme</b> .
<b>MHRA</b>	News, warnings, information and publications of <b>Medicines and Healthcare products Regulatory Agency (MHRA)</b> , responsible for ensuring efficacy and safety of medicines and medical devices in the <b>UK</b> .
<b>Health Canada</b>	Advisories, warnings, recalls, reports, publications, activities, legislations and guidelines from <b>Health Canada</b> , the Federal Department responsible for health-related issues in Canada.
<b>Thai FDA</b>	<b>Thai Food and Drug Administration</b> laws and regulations with respect to drugs, food, cosmetics and narcotics.
<b>HSA, Singapore</b>	Health Sciences Authority (HSA), the regulatory body of Singapore.
<b>DOH, Philippines</b>	<b>The Department of Health, Philippines</b> .
<b>Medsafe, New Zealand</b>	<b>Medsafe</b> , New Zealand Medicines and Medical Devices Safety Authority.

**NPCB, Malaysia**

Regulatory information, news and publications of **National Pharmaceutical Control Bureau, Malaysia.**

**DGMP, Belgium**

Guidelines and useful information to ensure safety, efficacy and quality of medicines, issued by **Directorate-General Medicinal Products, Belgium.**

**BfArM, Germany**

Licensing and registration guidelines for medicinal products laid down by **Federal Institute for Drugs and Medical Devices, Germany**

**SwissMedic**

**Swiss regulatory agency** for therapeutic products.

**MPA, Sweden**

Regulatory and surveillance guidelines issued by **Medical Products Agency, Sweden.**

**NAFDAC, Nigeria**

News, regulations and guidelines issued by **The National agency for Food Administration and Control (NAFDAC), Nigeria.**

## **Law and Acts**

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### **Background**

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

Laws related to Community Pharmacy

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



## **The Drugs and Cosmetics Act, 1940, and Rules, 1945**

The Drugs and Cosmetic Act, 1940, was enacted to regulate the import, manufacture, sale and distribution of drugs and cosmetics. The Act includes laws governing the setting up and operation of a pharmacy.

The emphasis of the Act is on self-regulation, but it can also be an effective tool in the hands of the regulatory agencies for quality management through licensing, periodic inspections to assess the extent of compliance, and initiating steps to continuously enhance the degree of compliance.

The Act intends to:

1. Prevent manufacture and distribution of sub standard drugs.
2. Control the manufacture, sale and distribution of drugs and ensure standard and quality drugs.
3. Monitor the licenses of premises from which medicines are sold/distributed.
4. Bring cosmetics in its purview, to regulate their import, manufacture, distribution and sale.

## **Narcotic Drugs and Psychotropic Substances Act and Rules,1985**

1. To consolidate and amend the law relating to narcotic drugs and psychotropic substances,
2. To make stringent provisions for the control and regulation of operations relating to narcotic drugs and psychotropic substances,
3. To provide for the forfeiture of property derived from, or used in, illicit traffic in narcotic drugs and psychotropic substances,
4. To implement the provisions of the International Convention on narcotic drugs and psychotropic substances, and matters connected therewith.

## **Drugs (Prices Control) Order, 1995**

The Drugs Prices Control Order,1995, is an order that lays down rules with respect to the fixation of prices of bulk drug and formulations.

The Order covers details like

1. Fixation of maximum sales prices of bulk drugs
2. Calculation of retail price of formulations
3. Fixation of retail price and ceiling price of scheduled formulations
4. Maintenance of records
5. Penalties for contravention of provision of the Order
6. Other details

The Drugs Price Control Order controls the prices of medicines, trying to make them available at fair prices.

## **The Consumer Protection Act,1986**

The Consumer Protection Act,1986, is a milestone in the history of the socio-economic legislation in the country. It is one of the most progressive and comprehensive pieces of legislation enacted for the protection of consumers.

1. The main objective of the Act is to provide better protection of the consumers.

2. The Act intends to provide simple, speedy and extensive redress of the consumer's grievances.
3. The Act enshrines certain rights of the consumers and provides for the setting up of Consumer Protection Councils in the Centre and the states. The objective of these Consumer Protection Councils will be to promote and protect the rights of the consumers.

The salient features of the Act are summed up as under:

4. The Act applies to all goods and services unless specifically exempted by the Central Government.
5. Since a pharmacy provides goods and services, it is also covered under this Act.
6. It covers all the sectors whether private, public or cooperative. The provisions of the Act are compensatory in nature.
7. It enshrines the following rights of the consumers:
  - i. The right to be protected against the marketing of goods, which are hazardous to life and property.
  - ii. The right to be informed about the quality, quantity, potency, purity, standard and price of goods so as to protect the consumer against unfair trade practices.
  - iii. The right to be assured, wherever possible, access to a variety of goods at competitive prices
  - iv. The right to be heard and to be assured that the consumer's interests will receive due consideration at appropriate forums.
  - v. The right to seek redress against unfair trade practices or unscrupulous exploitation of consumers, and
  - vi. The right to consumer education.

### **The Infant Milk Substitutes, Feeding Bottles and Infant Foods (Regulation of Production, Supply and Distribution) Act, 1992**

This Act provides for the regulation of production, supply and distribution of infant milk substitutes, feeding bottle sand infant foods with a view to protect and promote breast feeding and ensure the proper use of infant foods. Under this Act, "Health care system" means an institution or organization engaged, either directly or indirectly, in health care for mothers, infants or pregnant women, and includes health workers in private practice, in a **pharmacy**, in a **drugstore** and any association of health workers

According to this Act, no pharmacy should: -

1. Advertise, or take part in the publication of any advertisement, for the distribution, sale or supply of infant milk substitutes, infant foods or feeding bottles.
2. Give an impression or create a belief in any manner that feeding of infant milk substitute sand infant foods are equivalent to, or better than, mother's milk.
3. Take part in the promotion of infant milk substitutes, infant foods or feeding bottles.
4. Supply or distribute samples of infant milk substitutes or feeding bottles or infant food gifts of utensils or other articles.
5. Offer inducement of any other kind.

6. Use any health care system for displaying placards or posters relating to, or for the distribution of, materials for the purpose of promoting the use or sale of infant milk substitutes, infant foods or feeding bottles.
7. Demonstrate feeding with infant milk substitutes or infant foods to a mother of an infant or to any member of her family, except through a health worker. The health worker must clearly explain to the mother or to another member, the hazards of improper use of infant milk substitutes, infant foods or feeding bottles.
8. Fix the remuneration of any employee or give any commission to such employee on the basis of the volume of sale of such substitutes or bottles made by such employees.
9. Sell or otherwise distribute any infant milk substitute, infant foods and feeding bottles unless they conform prescribed standards.

### **The Drugs and Magic Remedies (objectionable Advertisements) Act, 1954**

This Act is enacted with a view to prevent objectionable and misleading advertisements in order to discourage self-medication and self-treatment, especially with regard to certain diseases of serious nature listed in the Act that can have a deleterious effect on the health of the community, and may affect the well being of the people.

The Drugs and Magic Remedies Act prohibits a person, from taking part in the publication of any advertisement referring to any drug which suggests the use of the drug for:

- a) Procurement of miscarriage of women, or prevention of conception in women.
- b) Maintenance or improvement of the capacity of human beings for sexual pleasure.
- c) The correction of menstrual disorder in women.
- d) The diagnosis, cure, mitigation, treatment or prevention of any venereal disease.

This Act prohibits directly or indirectly giving a false impression regarding the true character of the drug, making a false claim for it, or conveying any false or misleading information about it.

### **Prevention of Food and Adulteration Act 1954**

The Act makes provision for the prevention of adulteration of food.

The Prevention of Food and Adulteration Act is a social welfare legislation enacted to curb the widely spread evil of adulteration of food product and endangering national health and human life.

The Act covers details including

- ❖ General provisions as to food.
- ❖ Analysis of food.
- ❖ Public analysts and inspectors
- ❖ Packing and labeling of foods
- ❖ Prohibition and regulation of sales
- ❖ Additives present
- ❖ Other details
- ❖ **Definition**

- It is the publication of “Approved Drug Products with Therapeutic Equivalence Evaluations” by the Food and Drug Administration.
- It is prepared by The Orange Book Staff, Center for Drug Evaluation and Research.
- It identified drug products on the basis of safety and effectiveness by the Food and Drug Administration under the Federal Food, Drug, and Cosmetics Act.
- Drugs marketed only on the basis of safety or pre-1938 drugs.
- The list is independent of any current regulatory action against a drug product.
- The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons.
- The FDA does not recommend substituting drugs that have not been determined to be bioequivalent.
- Drugs that are not listed as bioequivalent should not be substituted for each other.

<b>YEAR</b>	<b>ACTION</b>
May 31, 1978	The Commissioner of the Food and Drug Administration sent a letter to officials of each state stating FDA’s intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.
January, 1979	The list was distributed (included only currently marketed prescription drug products approved by FDA through NDAs and ANDAs under the provisions of section 505 of the Act)
October 31, 1980	The final rule (includes FDA’s response to the public comments on the proposal) was published in the Federal Register (45 FR 72582). The list incorporated appropriate corrections and additions.

## **Objectives**

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

## **Orange Book**

### **Background**

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## **History**

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## **Objectives**

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## **Content of orange book**

### **1.INTRODUCTION**

#### **1.1. Content and Exclusion**

- ❖ Approved OTC drug products for those which are not marketed
- ❖ Approved prescription drug with therapeutic equivalence evaluations
- ❖ Drug products with Biologics Evaluation and Research
- ❖ List of approved products that have been discontinued from marketing

#### **1.2. Therapeutic Equivalence-Related Terms**

- ❖ Pharmaceutical equivalents
  - Contain the same active ingredient(s),
  - Have the same dosage form and route of administration, and
  - Identical in strength or concentration
  - May differ in shape, release mechanisms, and packaging
- ❖ Pharmaceutical alternatives
  - Contain the same therapeutic moiety but might differ in,
  - Salts, esters, or complexes form of the same moiety,
    - Different dosage forms,
    - Different strengths
- ❖ Therapeutic equivalents
- ❖ Therapeutic equivalents are expected to have the same clinical effect and safety profile.

- ❖ Drug products are considered therapeutic equivalents if they are all of the following
  - Pharmaceutical equivalents
  - Bioequivalent
  - Approved as safe and effective
  - Adequately labeled
  - Manufactured in compliance with current Good Manufacturing Practice regulations
- ❖ Bioequivalence and bio-availability
- ❖ Drug products are considered bioequivalent if they are pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to subjects at the same molar dose under similar experimental conditions
- ❖ Bioequivalence use to determine Therapeutic Equivalents

### **1.3. Statistical Criteria for Bioequivalence**

- ❖ In short Bioequivalence refers to equivalent release of the same drug substance from two or more drug products.
- ❖ The standard bioequivalence (PK) study is conducted in 24-36 adults using a two-treatment crossover study design.
- ❖ Alternately, a four-period, replicate design crossover study can also be used.
- ❖ The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure.
- ❖ Two situations are tested with this statistical methodology
- ❖ Pharmacokinetic parameters determine are AUC and Cmax.
- ❖ Two criteria include,
  - i. Whether a generic product(test), when substituted for a brand-name product (reference) is significantly less bio-available. (A limit of test-product average/reference-product average of 80%)
  - ii. Whether a brand-name product when substituted for a generic product is significantly less bio-available. (A limit of reference-product average/test-product average 125%)
- ❖ A difference of greater than 20% for each of the above tests was determined to be significant
- ❖ The confidence interval for both pharmacokinetic parameters, AUC and Cmax, must be entirely within the 80% to 125% boundaries cited above.

### **1.4. Reference Listed Drug**

- ❖ A reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.
- ❖ The aim of FDA is to avoid possible significant variations among generic drugs and their brand name counterpart.
- ❖ The reference listed drug is identified by the symbol “+” in the Prescription and Over-the-Counter (OTC) Drug Product Lists.
- ❖ List is available for oral dosage forms, injectables, ophthalmic, otics, and topical products.

## 1.5. General Policies and Legal Status

- ❖ The List contains public information and advice.
- ❖ It is not compulsory the drug products which may be purchased, prescribed, dispensed, or substituted for one another, nor does it, should be avoided.
- ❖ Exclusion of a drug product from the List does not necessarily mean that the drug product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products.
- ❖ Rather, FDA has not evaluated the safety, effectiveness, and quality of the drug product.

## 1.6. Practitioner/User Responsibilities

- ❖ Professional care and judgment should be exercised in using the list.
- ❖ Practitioner should be aware of the multi-source and single-source drug products.
  - i. Multisource Drug Product means those pharmaceutical equivalents available from more than one manufacturer. For such products, a therapeutic equivalence (TE) code is included and, in addition, product information is highlighted in bold face and underlined.
  - ii. Single-Source Drug Product means only one approved product is available for particular active ingredient, dosage form, route of administration, and strength. For such product no therapeutic equivalence code is included.
- ❖ Products on the List are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product:
- ❖ Applicants like Manufacture, Contract Manufacturer, Repackager, Distributor or Marketer.

## 1.7. Therapeutic Equivalence Evaluations Codes

- ❖ The coding system for therapeutic equivalence evaluations  
First letter: therapeutically equivalent to other pharmaceutically equivalent products  
Second letter: provide additional information on the basis of FDA's evaluations

## 1.8. Description of Special Situations

Example

Drugs	Description of Special Situations
Amino-acid and Protein Hydrolysate injections	These products differ in the amount and kinds of amino-acids they contain, and therefore, are not considered pharmaceutical equivalents. For this reason, these products are not considered therapeutically equivalent.

## 1.9. Therapeutic Equivalence Code Change for a Drug Entity

- ❖ Such changes occur in response to a petition or on its own initiative.
- ❖ Changes will generally occur when new scientific information affects the therapeutic equivalence of an entire category of drug products in the List.

## 1.10. Discontinued Section

- ❖ When the product has been discontinued from marketing,



- ❖ Are for military use,
- ❖ Or have had their approvals withdrawn for other than safety or efficacy reasons
- ❖ Drug Products for exportation

## **2.1. Key Sections for Using the Drug Product Lists**

- ❖ This contains illustrations, along with Drug Product Lists, indices, and lists of abbreviations and terms which facilitate their use.
  - i. Illustration: Depicts the format found in the Prescription Drug Product List.
  - ii. Drug Product Lists: The Prescription and OTC drug product lists, arranged alphabetically by active ingredient (s), contains product identification information (active ingredients, dosage forms, routes of administration, product names, application holders, strengths) for single and multiple ingredient drug products. Also shown are the application number and drug product number.
  - iii. Product Name Index.
  - iv. Product Name Index Listed by Applicant.
  - v. Uniform terms.

## **2.2. Drug Product Illustration**

- ❖ Active ingredient
- ❖ Dosage form: route of administration
- ❖ Trade or generic name
- ❖ Applicant
- ❖ Available strength of product
- ❖ Applicant number & product number
- ❖ Product number is for fda internal computer data use only

## **2.3. Therapeutic Equivalence Evaluations Illustration**

- ❖ Drug Product reviewed
- ❖ It includes only full approval products and not tentative approval products
- ❖ Drug Product of Repackager/Distributor is considered to be therapeutically equivalent to the Application Holder's product
- ❖ The new approvals and required changes in data are included in each subsequent edition. Even monthly cumulative supplements are published

## **Federal Register**

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### **Background**

Published by the Office of the Federal Register, National Archives and Records Administration (NARA), the Federal Register is the official daily publication for rules, proposed rules, and notices of Federal agencies and organizations, as well as executive orders and other presidential documents.



## **Federal Register**

The Federal Register is the official journal of the federal government of the United States that contains government agency rules, proposed rules, and public notices. It is published every weekday, except on federal holidays.

The final rules promulgated by a federal agency and published in the Federal Register are ultimately reorganized by topic or subject matter and codified in the Code of Federal Regulations (CFR), which is updated annually.

The Federal Register is compiled by the Office of the Federal Register (within the National Archives and Records Administration) and is printed by the Government Publishing Office. There are no copyright restrictions on the Federal Register; as a work of the U.S. government, it is in the public domain

## **History**

The Federal Register system of publication was created on July 26, 1935, under the Federal Register Act. The first issue of the Federal Register was published on March 16, 1936.<sup>[14]</sup> In 1946 the Administrative Procedure Act required agencies to publish more information related to their rulemaking documents in the Federal Register.

On March 11, 2014, Rep. Darrell Issa introduced the Federal Register Modernization Act (H.R. 4195), a bill that would require the Federal Register to be published (e.g., by electronic means), rather than printed, and that documents in the Federal Register be made available for sale or distribution to the public in published form. The American Association of Law Libraries (AALL) strongly opposed the bill, arguing that the bill undermines citizens' right to be informed by making it more difficult for citizens to find their government's regulations. According to AALL, a survey they conducted "revealed that members of the public, librarians, researchers, students, attorneys, and small business owners continue to rely on the print" version of the Federal Register. AALL also argued that the lack of print versions of the Federal Register and CFR would mean the 15 percent of Americans who don't use the Internet would lose their access to that material. The House voted on July 14, 2014, to pass the bill 386–0.

## **Contents**

The Federal Register provides a means for the government to announce to the public changes to government requirements, policies, and guidance.

- ❖ Proposed new rules and regulations
- ❖ Final rules
- ❖ Changes to existing rules
- ❖ Notices of meetings and adjudicatory proceedings
- ❖ Presidential documents including Executive orders, proclamations and administrative orders.
- ❖ Both proposed and final government rules are published in the Federal Register. A Notice of Proposed Rulemaking (or "NPRM") typically requests public comment on a proposed rule and provides notice of any public meetings where a proposed rule will be discussed. The public comments are considered by the issuing government agency, and the text of a final rule along with a discussion of the comments is published in the Federal Register. Any agency proposing a rule in the Federal Register must provide contact information for people and organizations interested in making comments to

the agencies and the agencies are required to address these concerns when it publishes its final rule on the subject.

- ❖ The notice and comment process, as outlined in the Administrative Procedure Act, gives the people a chance to participate in agency rulemaking. Publication of documents in the Federal Register also constitutes constructive notice, and its contents are judicially noticed.
- ❖ The United States Government Manual is published as a special edition of the Federal Register. Its focus is on programs and activities.

## **Format**

Each daily issue of the printed Federal Register is organized into four categories:

- ❖ Presidential Documents (executive orders and proclamations)
- ❖ Rules and Regulations (including policy statements and interpretations of rules by federal agencies)
- ❖ Proposed Rules (including petitions to agencies from the public)
- ❖ Notices (such as scheduled hearings and meetings open to the public and grant applications)

Citations from the Federal Register are [volume] FR [page number] ([date]), e.g., 71 FR 24924 (Apr. 7, 2006).

The final rules promulgated by a federal agency and published in the Federal Register are ultimately reorganized by topic or subject matter and re-published (or “codified”) in the Code of Federal Regulations (CFR), which is updated annually.

## **Availability**

Copies of the Federal Register may be obtained from the U.S. Government Publishing Office. Most law libraries associated with an American Bar Association–accredited law school will also have a set, as will federal depository libraries.

## **Free sources**

The Federal Register has been available online since 1994. Federal depository libraries within the U.S. also receive copies of the text, either in paper or microfiche format. Outside the U.S., some major libraries may also carry the Federal Register.

As part of the Federal E-Government eRulemaking Initiative, the web site Regulations.gov was established in 2003 to enable easy public access to agency dockets on rulemaking projects including the published Federal Register document. The public can use Regulations.gov to access entire rulemaking dockets from participating Federal agencies to include providing on-line comments directly to those responsible for drafting the rulemakings. To help federal agencies manage their dockets, the Federal Docket Management System (FDMS) was launched in 2005 and is the agency side of regulations.gov.

In April 2009, Citation Technologies created a free, searchable website for Federal Register articles dating from 1996 to the present.

GovPulse.us, a finalist in the Sunlight Foundation’s Apps for America 2, provides a web 2.0 interface to the Federal Register, including spark lines of agency activity and maps of current rules.

On July 25, 2010, the Federal Register 2.0 website went live. The new website is a

collaboration between the developers who created GovPulse.us, the Government Publishing Office and the National Archives and Records Administration.

On August 1, 2011, the Federal Register announced a new application programming interface (API) to facilitate programmatic access to the Federal Register content. The API is fully RESTful, utilizing the HATEOAS architecture with results delivered in the JSON format. Details are available at the developers page and Ruby and Python client libraries are available.

## **Paid sources**

In addition to purchasing printed copies or subscriptions, the contents of the Federal Register can be acquired via several commercial databases:

- ❖ Citation Technologies offers the complete Federal Register and Code of Federal Regulations (CFRs) through subscription-based web portals such as CyberRegs.<sup>[12]</sup>
- ❖ HeinOnline (1936): Full coverage available dating back to 1936 in an image-based searchable PDF format.
- ❖ LexisNexis (July 1, 1980): Searchable text format since 45 FR 44251.
- ❖ Westlaw (January 1, 1981): Searchable text format since 46 FR 1. The Unified Agenda and the official English text of the 1980 United Nations Convention on Contracts for the International Sale of Goods, which became effective January 1, 1988, are included. Sunshine Act Meeting Notices are not available prior to 1991. Unified Agenda documents are not available prior to October 1989.

## **Volumes of Federal Register**

### **Volumes 60 (1995) to present**

Available for download as an entire issue (in PDF and XML formats) or as smaller sections (in PDF and text formats).

View the Table of Contents for the most recent issue or for previous issues by clicking the TOC button for specific issues in browse. Sign up for a free email subscription of the daily Table of Contents.

XML files can be downloaded in bulk as a zip file by the year (volume) or month in the Bulk Data Repository. Information on the legal status, authenticity, and schema of the Federal Register XML renditions can be found in the User Guide Document - Federal Register XML Rendition.

Volumes 59 (1994) and older are digitized versions of historical issues of the Federal Register being made available as full issue PDF only. Note: Volume 59 (1994) has entire issues available in PDF format only, and smaller sections available in text format only. These digitized volumes include all issues and parts of the official printed edition. (See below for more information on searching the Digitized Federal Register.)

- ❖ **Volume 59 (1994)** issues are a special case. They originally existed in the system in text format only, but now also have PDF format available for the entire issue. Smaller sections are available only in text format.

The **Federal Register Index** and **List of CFR Sections Affected (LSA)**

**Gov info** provides a tool to easily find **CFR Parts Affected** from the Federal Register. Learn more about this tool below.

To find a **more recent, unofficial issue** of the Federal Register, view the Public Inspection issue online at [www.federalregister.gov](http://www.federalregister.gov), a service of the National Archives and Records Administration's Office of the Federal Register.

You may be able to find new rules and regulations on an agency's website before it is published in the Federal Register, but this is not considered the official version and the effective date is generally based on when it is published in the Federal Register.

❖ **GPO's Online Bookstore** has the following available for purchase:

Individual issues in print and microfiche

Annual subscription in print and microfiche

Federal Register Index in print and microfiche

## **Organization of federal register**

### **Table of Contents and Preliminary Pages**

This section of the Federal Register contains a comprehensive alphabetical listing by agency name of all documents in the issue. Under each agency, the documents are arranged by classification—Rules, Proposed Rules, or Notices. Each entry includes the page number where the document begins and a brief description of the document.

If Presidential Documents appear in the Federal Register they are listed in alphabetical order in the Contents under the heading "Presidential Documents". Appearing at the end of the Contents is a list of separate parts published in the issue, if applicable. The documents appearing in the separate part are also listed under the agency in the table of contents.

Also appearing in the preliminary pages (Contents Section) of each day's Federal Register is a list of the CFR Parts Affected in This Issue. Under each CFR title the parts affected by the rules and proposed rules in the issue are listed along with the page numbers where relevant documents begin.

The Reader Aids section of the Federal Register is designed to help the reader find specific information in the Federal Register system, as distinguished from the finding aids in the preliminary pages (Contents section) which are more oriented to one particular issue of the Federal Register.

### **Rules and Regulations Section**

This section of the Federal Register contains final rules and regulations: regulatory documents having general applicability and legal effect. Most rules are keyed to and codified in the Code of Federal Regulations (CFR). A document which amends text must include the changes to the CFR and state the effective date for any change.

Each document begins with a heading that includes the name of the issuing agency (and sub-agency if appropriate), the CFR title and part(s) affected, and a brief description of the specific subject of the document. In some cases, an agency includes a docket number, which identifies the document within the agency's internal filing system. A Regulation Identifier Number (RIN) may also be included.

This section also contains interim rules that are issued without prior notice and are effective immediately; the interim rule is designed to respond to an emergency situation and is usually followed by a final rule document which confirms that the interim rule is final, addresses comments received, and includes any further amendments. Additionally, this section

includes documents that have no regulatory text and do not amend the CFR, but either affects the agency's handling of its regulations or are of continuing interest to the public in dealing with an agency. In this category are general policy statements and interpretations of agency regulations. These documents have the CFR headings (title and part), but do not contain any codified language.

The terms "rules" and "regulations" have the same meaning within the Federal Register publication system.

### **Proposed Rules Section**

This section of the Federal Register contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

Many proposed rules are documents that suggest changes to agency regulations in the Code of Federal Regulations (CFR) and request public comment on those suggested changes. This section also contains documents relating to previously published proposed rules, extending the comment period, announcing a public hearing, making available supplemental information, withdrawing a proposed rule, or correcting a previously published proposed rule.

This section includes advanced notices of proposed rulemaking, which describe a problem or situation and the anticipated regulatory action of the agency and seek public response concerning the necessity for regulation and the adequacy of the agency's anticipated regulatory action. Additionally, many agencies voluntarily publish proposed changes to procedural rules, interpretative rules and agency policies to gather public comments.

Each document begins with a heading that includes the name of the issuing agency (and sub-agency if appropriate), the CFR title and part(s) affected, and a brief description of the specific subject of the document. In some cases, an agency docket number, which identifies the document within the agency's internal filing system. A Regulation Identifier Number (RIN) may also be included. Instructions for filing comments and the date by which comments must be filed are provided.

The terms "rules" and "regulations" have the same meaning within the Federal Register publication system.

### **Notices Section**

This section of the Federal Register contains documents other than rules or proposed rules that are applicable to the public. Notices of hearings and investigations, committee meetings, agency decisions and rulings, delegations of authority, issuances or revocation of licenses, grant application deadlines, availability of environmental impact statements, filing of petitions and applications, and agency statements of organization and functions are examples of documents appearing in this section.

### **Presidential Documents Section**

This section of the Federal Register contains documents signed by the President and submitted to the Office of the Federal Register for publication. Presidential documents include Proclamations and Executive Orders, as well as other documents such as determinations, letters, memorandums, and reorganization plans. The documents are compiled annually in title 3 of the Code of Federal Regulations (CFR).

## **Sunshine Act Meetings**

This section of the Federal Register contains notices of meetings published under the “Government in the Sunshine Act” (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

In recognition of the public’s right to the fullest possible information about the Federal decision-making process, the Government in the Sunshine Act requires that meetings of Government agencies be open to the public, with certain specified exceptions. The Act also requires that public announcement be made in the Federal Register of the time, place, and subject matter of the meeting, the name and telephone number of the agency official to contact for more information, and whether the meeting is open or closed to the public.

## **Reader Aids**

This section of the Federal Register is designed to help the reader find specific information in the Federal Register system, as distinguished from the finding aids in the preliminary pages (Contents section) which are more oriented to one particular issue of the Federal Register.

- ❖ Information and Assistance. Appearing first is the listing of Office of the Federal Register telephone numbers to call for specific information.
- ❖ Federal Register Pages and Dates. This is a table of the inclusive page numbers and corresponding dates for the current month’s Federal Register.
- ❖ CFR Parts Affected During the Current Month. This is a cumulative list of Code of Federal Regulations (CFR) parts affected by rules and proposed rules published in the Federal Register during the current month.

## **Corrections Section**

This section of the Federal Register contains editorial corrections of previously published Presidential, Rule, Proposed Rule, and Notice documents. These corrections are prepared by the Office of the Federal Register to correct typographical or clerical errors made in the printing of the Federal Register. Agency prepared corrections are issued as signed documents and appear in the appropriate document categories elsewhere in the issue.

## **CFR Parts Affected from the Federal Register**

The Federal Register contains rules and regulations which are regulatory documents having general applicability and legal effect. Most rules are codified in the Code of Federal Regulations (CFR).

Browse CFR Parts Affected from the Federal Register to find final and proposed rules that affect the CFR and have been published in the Federal Register within the past 24 hours, week, month, or within a specific date range.

CFR Parts Affected is also contained in the Reader Aids section of each Federal Register issue.

## **Unified Agenda**

The Unified Agenda, as published in the Federal Register, is available on a separate page on **govinfo**. The complete Unified Agenda is available to the public at [Reginfo.gov](http://Reginfo.gov).

The Unified Agenda of Federal Regulatory and Deregulatory Actions (Unified Agenda) provides uniform reporting on the actions administrative agencies plan to issue in the near and long term. Executive Order 12866 “Regulatory Planning and Review,” signed September 30, 1993 (58 FR 51735), and Office of Management and Budget memoranda implementing section 4 of that Order establish minimum standards for agencies’ agendas, including specific



types of information for each entry. Each edition of the Unified Agenda includes regulatory agendas from Federal entities that currently have regulations under development or review. Agencies of the United States Congress are not included. Fall editions of the Unified Agenda include The Regulatory Plan, which presents agency statements of regulatory priorities and additional information about the most significant regulatory activities planned for the coming year.

All editions of the Unified Agenda through the spring 2007 edition were published in their entirety in the Federal Register. Beginning with the fall 2007 edition, the Agenda published in the Federal Register is limited, in general, to agency regulatory flexibility agendas and The Regulatory Plan. Agency regulatory flexibility agendas, which are required by the Regulatory Flexibility Act (PDF) to be published in the Federal Register, include only those rules that may have a significant economic impact on a substantial number of small entities and entries that have been selected for periodic review under section 610 (PDF) of the Regulatory Flexibility Act.

The Unified Agenda is compiled by the Regulatory Information Service Center, a component of the U.S. General Services Administration, in cooperation with the Office of Management and Budget's Office of Information and Regulatory Affairs. Applicable agendas are then published by the Office of the Federal Register, National Archives and Records Administration (NARA) in the Federal Register. The Regulatory Information Service Center assigns a Regulation Identifier Number (RIN) to identify each regulatory action listed in the Unified Agenda.

## Code of federal regulatory

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### Background

The Code of Federal Regulations (CFR) annual edition is the codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government.

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

Note: In the official paper bound version and the official PDF versions of 2007 edition of Title 49 volume 6 parts 400-599, the header incorrectly reads "(10-1-06 Edition)" and should have read "(10-1-07 Edition)".

The CFR on **govinfo** is current with the published print version of the CFR. When the print editions are released, the online version is also made available. If a CFR Title or volume is not listed in the CFR browse, that volume has not yet been published.

The 50 subject matter titles contain one or more individual volumes, which are updated once each calendar year, on a staggered basis. The annual update cycle is as follows:

Titles 1-16 are revised as of January 1

Titles 17-27 are revised as of April 1

Titles 28-41 are revised as of July 1

Titles 42-50 are revised as of October 1

**govinfo** currently contains titles from **1996 to the present**. CFR volumes are added concurrent with the release of the paper editions. When revised CFR volumes are added, the prior editions remain on **govinfo** as a historical set. **Bulk data downloads of Code of Federal Regulations XML files** are available to the general public via Data.gov and GPO's Bulk Data Repository. Information on the legal status, authenticity, and schema of the Code of Federal Regulations XML renditions can be found in the User Guide Document - Code of Federal Register XML Rendition. To see **more recently updated** titles of the CFR, visit the electronic Code of Federal Regulations (e-CFR), a regularly updated, unofficial editorial compilation of CFR material and Federal Register amendments. The eCFR is updated on a daily basis. To see a cumulative list of CFR sections that have been changed at any time since each CFR title was last updated, view the **List of CFR Sections Affected (LSA)**. To find final and proposed rules that affect the CFR and have been published in the Federal Register within the past 24 hours, week, month, or within a specific date range, browse the **CFR Parts Affected from the Federal Register**

## Organization

The CFR is divided into 50 titles that represent broad areas subject to Federal regulation. Each title is divided into chapters, which usually bear the name of the issuing agency. Each chapter is further subdivided into parts that cover specific regulatory areas. Large parts may be subdivided into subparts. All parts are organized in sections, and most citations to the CFR refer to material at the section level.

## Structure of a CFR citation

The following describes how information is contained in a CFR citation.

- ❖ **Title:** The numeric value to the left of "CFR"
- ❖ **Part:** The numeric value to the right of "CFR" and preceding the period (".")
- ❖ **Section/Subpart:** The numeric value to the right of the period (".") A subpart is a letter of the alphabet (A-Z) that is used to retrieve an entire subpart of the CFR rather than many individual sections. For example: Subpart E.
- ❖ **Revision Year:** Four-digit year from the "Revised as of" text represents the year being cited. The revision year is not always available when the CFR is cited.
- ❖ Example: 21 CFR 310.502 Revised as of April 1, 1997
- ❖ Title: 21
- ❖ Part: 310
- ❖ Section: 502
- ❖ Year: 1997

## Parallel Table of Authorities and Rules for the Code of Federal Regulations and the United States Code

The Parallel Table of Authorities and Rules lists rulemaking authority (except 5 U.S.C. 301) for regulations codified in the Code of Federal Regulations. Also included are statutory citations which are noted as being interpreted or applied by those regulations.



The table is divided into four segments and within each segment the citations are arranged in numerical order:

1. For the United States Code citations, by title and section;
2. For the United States Statutes at Large citations, by volume and page number;
3. For public laws citations, by number;
4. For Presidential documents (Proclamations, Executive orders, and Reorganization plans) citations, by document number. Entries in the table are taken directly from the rulemaking authority citation provided by Federal agencies in their regulations. Federal agencies are responsible for keeping these citations current and accurate. Because Federal agencies sometimes present these citations in an inconsistent manner, the table cannot be considered all-inclusive. The portion of the table listing the United States Code citations is the most comprehensive, as these citations are entered into the table whenever they are given in the authority citations provided by the agencies. United States Statutes at Large and public law citations are carried in the table only when there are no corresponding United States Code citations given. Beginning in 2017, the table is available in volumes of the CFR Index and Finding Aids publication on **govinfo**. You can download the entire CFR Index and Finding Aids volume or just the Parallel Table of Authorities and Rules.

## Searching the Code of Federal Regulations

You can find and search the Code of Federal Regulations by:

- ❖ Using **Basic Search** for keyword and metadata fielded searches,
- ❖ Using **Advanced Search**; fields specific to the CFR will display after you select Code of Federal Regulations in the Refine by Collection column,
- ❖ Using **Citation Search** to retrieve a single Code of Federal Regulations document in PDF format if you know the Volume and Page of the document,
- ❖ **Refining search results** by clicking on links in the Refine Your Search panel on the left-hand side of the page (the sections under Refine Your Search correspond to the metadata available for the documents), and
- ❖ **Browsing** the Code of Federal Regulations browse page.
- ❖ **General govinfo Search Tips**
- ❖ **Search Examples**
- ❖ **Search by Citation**- For example, 7 CFR 1951.7 from 2016.
- ❖ Using Basic Search, enter: collection: cfr and citation:"7 CFR 1951.7" and publishdate:2016
- ❖ Using Advanced Search, select Code of Federal Regulations under Refine by Collection, then under Search In select Citation in the first box and enter "7 CFR 1951.7" in the second box
- ❖ Using Citation Search, select Code of Federal Regulations from Select Collection box, select 2016 from Select Year box, select 7 from Select Title Number box, and enter 1951.7 in Section box
- ❖ **Search by Title Number**- For example, CFR documents from Title 7.
- ❖ Using Basic Search, enter: collection: cfr and cfrtitlenum:7

- ❖ Using Advanced Search, select Code of Federal Regulations under Refine by Collection, then under Search In select CFR Title Number in the first box and enter 7 in the second box
- ❖ **Search by Title and Part Number-** CFR documents from Title 7, Part 1951.
- ❖ Using Basic Search, enter: collection: cfr and cfrtitlenum:7 and cfrpartnum:1951
- ❖ Using Advanced Search, select Code of Federal Regulations under Refine by Collection, then under Search In select CFR Title Number in the first box, enter 7 in the second box, click + Additional Criteria, select CFR Part Number from the resulting box, and enter 1951 in the next box
- ❖ **Search by Keyword-** For example, Code of Federal Regulations documents with “emissions” in the full text of the publication.
- ❖ Using Basic Search, enter: emissions and collection: cfr
- ❖ Using Advanced Search, select Code of Federal Regulations under Refine by Collection, then under Search In enter emissions in the second box
- ❖ **Sample Code of Federal Regulations URLs**
- ❖ **Govinfo** uses two key pieces of information to construct predictable URLs to documents and Details pages:
- ❖ Granule ID for the Code of Federal Regulations is used to identify the specific section, part, subpart, chapter, or subchapter within a volume of the publication.
- ❖ Package ID is used to identify an individual volume of the publication.

## Metadata Fields and Values

Metadata fields and values can be used to increase the relevancy of your searches. The metadata fields available for the Code of Federal Regulations are listed in the table below. Metadata fields and values are used throughout govinfo for

- ❖ Narrowing Your Search,

Identifier	Structure/Metadata Field	Examples
<b>Granule ID</b>	Chapter CFR- <b>{ Year}</b> -title {CFR Title Number}-vol {CFR Volume Number}-chap {Chapter Identifier} Subchapter CFR- <b>{ Year}</b> -title {CFR Title Number}-vol {CFR Volume Number}-chap {Chapter Identifier}-sub chap {Subchapter Identifier} Part CFR- <b>{ Year}</b> -title {CFR Title Number}-vol {CFR Volume Number}-part {Part Number} Subpart CFR- <b>{ Year}</b> -title {CFR Title	CFR-2008-title39-vol1-chapI CFR-2008-title39-vol1-chapI-subchap B CFR-2008-title39-vol1-part20 CFR-2008-title39-vol1-part777-subpartA CFR-2008-title39-vol1-sec20-2

	Number}-vol {CFR Volume Number}-part {Part Number}-subpart {Subpart Identifier}Section CFR-{Year}-title {CFR Title Number}-vol {CFR Volume Number}-sec {Part Number}-{Section Identifier - only the portion after the period in the citation} Note: When a chapter, subchapter, part, section, or subpart is split over multiple volumes, combined files are not available and direct links to documents must be accessed at a more granular level.	
<b>Package ID</b>	CFR-{Year}-title {CFR Title Number}-vol {CFR Volume Number}	CFR-2008-title39-vol1

- ❖ Browsing Government Publications,
- ❖ Field Operators,
- ❖ Advanced Search, and
- ❖ Display on Details Pages.

Metadata fields and values can be entered into the Basic Search box using field operators. The field operators available for the Code of Federal Regulations are listed in the table below, along with examples for each metadata field. Using Field Operators

Some of these metadata fields are made available for use in Advanced Search. The metadata values can be entered in the same format for the fields available on the Advanced Search Page. Using Advanced Search

### Code of Federal Regulations Related Resources

- ❖ List of CFR Sections Affected - Proposed, new, and amended Federal regulations that have been published in the Federal Register since the most recent revision date of a CFR title.
- ❖ Browse CFR Parts Affected from the Federal Register - Final and proposed rules that

Metadata Field Display Name	Metadata Field Definition	Field Operator	Field Operator Example(s)
<b>Collection</b>	The collection to which the document belongs. Typically, the same as the publication or series.	Collection	collection: cfr Note: "cfr" is used for the Code of Federal Regulations

<b>Metadata Field Display Name</b>	<b>Metadata Field Definition</b>	<b>Field Operator</b>	<b>Field Operator Example(s)</b>
<b>Government Author</b>	The names of the Government organizations responsible for authoring or assembling the document.	government author:	government author: "office of the federal register"
<b>Publication Date</b>	The date the document was first made available to the public.	publish date:	publish date: 2016-01-01Date format is YYYY, YYYY-MM, or YYYY-MM-DD
<b>Language</b>	The language code of the original document, from the ISO639-2b standard.	language:	language
<b>Former Package ID</b>	The document ID of the "package."	mods: identifier:(@type:"former package identifier": _____")	mods: identifier:(@type:"former package identifier": "44CFR")
<b>SuDoc Class Number</b>	The SuDoc class number from the U.S. Superintendent of Documents which classifies Government publications by publishing agency.	sudocclass:	sudocclass:"AE 2.106/3:"Note: The SuDoc Class Numbers are at the class stem level, not the book number level.
<b>Ingestion Date</b>	The date the document was ingested into the preservation repository.	ingest date:	ingest date : 2009-12-29 Date format is YYYY-MM-DD
<b>Electronic Location (URL)</b>	The URL where the document or the document in context (the content detail page) is located.	url:	url:pkg/CFR-2016-title1-vol1/pdf/CFR-2016-title1-vol1-sec1-1.pdf
<b>Publisher</b>	The government organization who publishes the document or publication. Not typically the Government Publishing Office (who serves as the printer and distributor), except in the case of Congressional publications.	publisher:	publisher: "Office of the Federal Register, National Archives and Records Administration"

<b>Metadata Field Display Name</b>	<b>Metadata Field Definition</b>	<b>Field Operator</b>	<b>Field Operator Example(s)</b>
<b>Branch</b>	The branch of Government responsible for the document's contents.	branch:	branch: executive Note: Possible Values: Executive, Legislative, Judicial
<b>Type of Resource</b>	The media type for the document, typically "text". Defined as part of the Library of Congress MODS standard.	Type of resource:	typeofresource:text
<b>WAIS Database Name</b>	The name of the WAIS database to which the document belonged in the former GPO Access system.	waisdbname:	waisdbname:2016_cfr_1v1
<b>Record Origin</b>	How the record was originally generated. Typically, "machine generated."	record origin:	record origin: "machine generated"
<b>Title</b>	The title of the publication.	title:	title: "agriculture"
<b>CFR Title Number</b>	CFR Title Number, an integer number from 1 to 50.	cfrtitlenum:	cfrtitlenum:7
<b>CFR Part Number</b>	CFR part number, an integer number of the part within the title.	cfrpartnum:	cfrpartnum:1951
<b>CFR Section Number</b>	The CFR section number.	cfrsectionnum:	cfrsectionnum:94.1
<b>Heading</b>	Search for the heading.	heading:	heading: "part 2" heading: "subpart I" heading: "chapter 9"
<b>CFR Subject Group</b>	The subject group for the sections, typically used for very large parts, such as the Internal Revenue part on income taxes.	cfr subject:	cfr subject:"income tax"
<b>CFR Citation</b>	Citation references to the Code of Federal Regulations.	cfr citation:	cfrcitation:"40 CFR Part 32"

<b>Metadata Field Display Name</b>	<b>Metadata Field Definition</b>	<b>Field Operator</b>	<b>Field Operator Example(s)</b>
<b>CFR Part Heading</b>		cfrpartheading:	cfrpartheading:"part 2"
<b>CFR Part Title</b>		cfrparttitle:	cfrparttitle:"capital construction fund"
<b>CFR SubPart Heading</b>		cfrsubpartheading:	cfrsubpartheading:"subpart b"
<b>CFR SubPart Title</b>		cfrsubparttitle:	cfrsubparttitle:"registration of pilots"
<b>CFR Chapter Heading</b>		cfrchapterheading:	cfrchapterheading:"chapter 2"
<b>CFR Chapter Title</b>		cfrchaptertitle:	cfrchaptertitle:"rural housing service"
<b>CFR Appendix Heading</b>		cfrappheading:	cfrappheading:"appendix a"
<b>CFR Appendix Title</b>		cfrapptitle:	cfrapptitle:"alternate foods for meals"
<b>Book Contents Statement</b>		cfrbookcontents:	cfrbookcontents:"parts 1 to 199"
<b>CFR Authority</b>		cfrauthority:	cfrauthority:"44 U.S.C. Ch. 35"
<b>CFR Source</b>		cfrsource:	cfrsource:"38 FR 25170"
<b>CFR Cross Reference</b>		cfrxref:	cfrxref:"42 CFR 110"
<b>CFR Editorial Notes</b>		cfreditorial:	cfreditorial:"70 FR 57994"
<b>CFR Citation Text:</b>		cfrcitationtext:	cfrcitationtext:"60 FR 13895, Mar. 15, 1995, as amended at 69 FR 42100, July 14, 2004"
<b>Citation</b>	The GPO standard method for searching citation references from the selected publication.	citation:	citation:"9 CFR 2.2"
<b>Congressional Bills Citation</b>	Citation references to Congressional Bills.	billscitation:	billscitation:"h.r. 1"

<b>Metadata Field Display Name</b>	<b>Metadata Field Definition</b>	<b>Field Operator</b>	<b>Field Operator Example(s)</b>
<b>Congressional Report Citation</b>	Citation references to Congressional Reports.	crptcitation:	crptcitation:"S. Rept. 99-296"
<b>Public and Private Law Citation</b>	Citation references to Public or Private Laws.	plawcitation:	plawcitation:"public law 71-126"
<b>United States Code Citation</b>	Citation references to the United States Code.	uscodecitation:	uscodecitation:"42 U.S.C. 3121"
<b>Statutes at Large Citation</b>	Citation references to Statutes at Large.	statute citation:	statutecitation:"70 Stat. 1046"
<b>Federal Register Citation</b>	Reference to the Federal Register, in standard citation format.	frcitation:	frcitation:"52 FR 49386"
<b>Reference Citation</b>	Reference to another document within the text of a document.	refcitation:	refcitation:"42 U.S.C. 3121"

affect the CFR and have been published in the Federal Register within the past 24 hours, week, month, or within a specific date range.

- ❖ Electronic Code of Federal Regulations (e-CFR) - A regularly updated, unofficial editorial compilation of CFR material and Federal Register amendments produced by the National Archives and Records Administration's Office of the Federal Register and the Government Publishing Office
- ❖ Regulations.gov - Find, review, and submit comments on Federal rules that are open for comment and published in the Federal Register. Managed by the U.S. Environmental Protection Agency eRulemaking Program Management Office.
- ❖ A Guide to the Rulemaking Process (PDF) - Prepared by the Office of the Federal Register, National Archives and Records Administration.
- ❖ Contact your local Federal Depository Library - Including issues prior to 1996 using the Federal Depository Library Directory.
- ❖ Purchase individual CFR titles in print - From GPO's Online Bookstore
- ❖ Download the CFR (Annual) in bulk XML - From GPO's bulk data repository.
- ❖ Parallel Table of Authorities and Rules - For the Code of Federal Regulations and the United States Code
- ❖ Federal Register - Published by the Office of the Federal Register, National Archives and Records Administration (NARA), the Federal Register is the official daily publication for rules, proposed rules, and notices of Federal agencies and organizations, as well as executive orders and other presidential documents
- ❖ FederalRegister.gov - Unofficial, HTML (XML-based) edition of the daily Federal Register provided by the Office of the Federal Register, National Archives and Records Administration

- ❖ [Reginfo.gov](http://Reginfo.gov) - Provides reliable, transparent information about regulations under development

## Purple book

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### Background

The Purple Book is a compendium of FDA-approved biological products and their bio-similar and interchangeable products. It is similar to the Orange Book, which is a listing of approved generic drugs with therapeutic equivalency to brand products. Information for each product listed in the Purple Book includes its BLA tracking number, product name, product proprietary name, date of licensure, date of first licensure, reference product exclusivity expiration date, indication as to whether the product is interchangeable (I) or bio-similar (B), and whether the product was withdrawn from the market.

Evaluations”, the purpose of the purple book is:

1. To assist users, understand if a biological product has been approved by FDA under the PHS Act with a reference product (already approved biological product)
2. To help identify if there is any exclusivity for a given reference product. The Purple Book includes two lists of biologics. The first list includes biologics approved by the FDA’s Center for Drug Evaluation and Research (CDER) and the second list includes biologics approved by the Center for Bio-logic Evaluation and Research (CBER).

The book also includes the following information about the biologics:

- ❖ BLA Number
- ❖ Non-Proprietary Product Names
- ❖ Proprietary Product Names
- ❖ Date the Product was approved in the Market
- ❖ Date of the first Licensure
- ❖ Whether the Product is Bio-similar or Interchangeable
- ❖ Reference Product with an Expiry Date
- ❖ Whether the Product is withdrawn from the Market





## APPENDIX A



### Practice Question

1. What is Regulatory Affairs?
2. What are the goals of Regulatory Affairs Professionals?
3. What are the Roles of Regulatory Affairs professionals?
4. What is an Investigational New Drug (IND) application?
5. What is a New Drug Application?
6. What is an Abbreviated New Drug Application (ANDA)?
7. What are the different stages of drug discovery?
8. What is the generic drug? Define and explain process of generic drug development.
9. Define clinical trial and explain in brief about different phases of clinical trial.
10. Give the brief overview on regulatory authorities of following-
  - A. India
  - B. United state
  - C. European union
  - D. Japan
  - E. Canada
11. What is the procedure for export of pharmaceutical products?
12. Write in detail about-
  - A. common technical document
  - B. Electronic common technical document
  - C. ASEAN common technical document
13. Define following-
  - A. Institution review board/ independent ethical committee
  - B. Sponsor
  - C. Investigators
14. What is orange book?
15. Give detail about code of federal regulation.
16. Write in brief about purple book.

## About the Author



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