

# **NON CLINICAL DRUG DEVELOPMENT**

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## **INTRODUCTION:**

- The non-clinical (or pre-clinical) development phase primarily aims to identify which candidate therapy has the greatest probability of success, assess its safety, and build solid scientific foundations before transition to the clinical development phase.
- Also, during the non-clinical development phase, the candidate compound should meet non-medical objectives, including defining the intellectual property rights and making enough medicinal product available for clinical trials.
- The non-clinical development of a medicine is complex and regulatory-driven.

- The studies in non-clinical development are performed:
- In silico: ‘performed on computer or via computer simulation’, e.g. predicting the toxicology profile of a product using its chemical structure from data-based approaches.
- In vitro (Latin for ‘within the glass’): performing a procedure in a controlled environment outside of a living organism, e.g. use of hepatocyte (cells from the liver) cultures for metabolism studies.
- In vivo (Latin for ‘within the living’): experimentation using a whole, living organism as opposed to tissues or cells, i.e. animals, humans or plants.

## Objectives

- Once a candidate compound is identified, the non-clinical development should start answering the following questions, and answers will come from specific assessments/studies:
- Does it work? → efficacy assessment
- How will it be delivered and how will the body react? → profiling
- Is it safe? → toxicology/safety
- Is the manufacture viable and controllable?
- Non-clinical development activities can continue throughout the life-cycle of the product, although the earlier these questions are answered, the easier it is to identify the profile of the patient who will benefit most.

## **Non-clinical regulatory guidelines**

- There are many players involved in the development of medicines, and each organization or institution follows their own set of rules.
- For instance, companies have their Standard Operating Procedures (SOP).
- In addition to Good Clinical Practice provisions, guidelines can be consulted at the European Medicines Agency (EMA) website.
- They are either general or more specific addressing scientific and technical aspects (e.g. specific to required toxicology studies).
- They must be strictly followed for any new marketing authorization application; any deviation must be justified.

# **Types of non-clinical study**

- **Pharmacodynamics (PD)**
- **Pharmacokinetics (PK)**
- **Toxicology**

# Non-clinical outcomes that can stop development of the compound

- A primary purpose of [non-clinical studies](#) is to discover target organ [toxicity](#), and from this information stop the development of the [compound](#) or use this information for monitoring possible toxicities in humans.
- The non-clinical outcomes that can stop the development of a new medicine are:
- Discovery of target organ [toxicity](#), e.g. if a [compound](#) is hepatotoxic (toxic to the liver) in animal, further development may be reconsidered, although predictive value of animal studies may be questioned.
- Identification of poor [PK](#) properties, e.g. if a product is doesn't get to its target, or if it accumulates, or generates [toxicity](#). This also explains why early [ADME](#) studies are performed, in order to optimise selection of successful product candidates.

# Specifics of non-clinical development for biological compounds

- Biologics are complex in comparison to small molecules (e.g. large molecules, tissues, cells, proteins). Although the principles are the same, the non-clinical development plan for biologics must be adapted, following a case-by-case approach.
- However, standard development plans are also emerging for biologics, distinct from those well established for small molecules, driven by lessons learned from experience and new regulatory guidance.

# Non-clinical development in CTD modules

## INVESTIGATIONAL NEW DRUG (IND)

- Investigational New Drug is defined under 21 CFR 312.3(b) as ‘ a new drug or biological drug that is used in clinical investigation’.
- The term also includes a biological product used in-vitro for diagnostic purposes.
- After pre-clinical investigations when the new molecule has been screened for pharmacological activity and acute toxicity potential in animals the sponsor requires permission from FDA for its clinical trials in humans.
- The sponsor submits the application for conduct of human clinical trials called Investigational New Drug (IND) application to FDA or DCGI .

- Once IND application is submitted , the sponsor must wait for 30 days before initiating any clinical trial.
- Clinical trials in humans can begin only after IND is reviewed by the FDA and a local institutional review board (IRB).
- IRBs approve clinical trial protocol, informed consent of all participants and appropriate steps to prevent subjects from harm.
- **TYPES OF INDs**
  - **COMMERCIAL INDs:** These are applications that are submitted primarily by the companies to obtain marketing approval for a new product.
  - **NONCOMMERCIAL (Research)INDs:** These INDs are filed for noncommercial research.

These are :

### **1) Investigator's IND:**

- It is submitted by a physician who both initiates and conducts an investigation and who also administers and dispenses the IP. A physician might submit a research IND to propose studying an unapproved drug or an approved drug for new indications or in new patient population.

### **2) Emergency Use IND :**

- This IND allows FDA to allow the use of an experimental drug in an emergency situation that does not allow submission of an IND in accordance with 21 CFR Sec312.23 or Sec 312.34. It can also be used for patients who do not meet the criteria of an existing study protocol or if an approved study protocol does not exist.

### **3) Treatment IND-**

- Also called Expanded Access IND This IND may be submitted for experimental drugs showing promise in clinical testing of serious and immediately life threatening conditions while the final clinical work is conducted and the FDA review takes place (21 CFR 312.34).

## Criteria for IND application

- ✓ A new indication
- ✓ Change in the approved route of administration or dosage level.
- ✓ Change in the approved patient population (vulnerable subjects e.g. pediatrics, elderly, HIV +ve, immunocompromised)
- ✓ Significant change in the promotion of an approved Drug.

# NEW DRUG APPLICATION (NDA)

- The New Drug Application is the vehicle through which the drug sponsors formally propose FDA or DCGI to approve a new investigational drug for sale and marketing after Phase IIIA Pivot trials.
- The official definition of New Drug is in Sec 201(p) of Federal Drug, Food and Cosmetics Act as;
- Any new drug , the composition of which is such that it is not recognized among experts qualified by scientific training as safe and effective for use under prescribed, recommended or suggested conditions.
- Any drug the composition of which is such that it as a result of investigations to determine safety and efficacy for use has become recognized, but which has not, otherwise in such investigations been used to a material extent.

- The following letter codes describe the review priority of the drug;
  - **S-Standard review:** For drugs similar to currently available drugs
  - **P-Priority review:** For drugs that represent significant advances over existing treatments.

## **Classification of drugs in NDA**

- Center of drug evaluation and Research(CDER) classifies new drug applications according to the type of drug being submitted and its intended use:
  - a. New molecular entity
  - b. New salt of previously approved drug
  - c. New formulation of previously approved drug
  - d. New combination of two or more drugs
  - e. Already marketed drug product- Duplication (i.e., new manufacturer)
  - f. New indication (claim) for already marketed drug (includes switching marketing status from prescription to OTC)
  - g. Already marketed drug product ( no previous approved NDA) S

# ABBREVIATED NEW DRUG APPLICATION (ANDA)

- Generic drug applications are referred to Abbreviated New Drug Application.
- Pharmaceutical companies must submit ANDAs and receive FDA's approval before marketing new generic drugs according to 21CFR 314.105(d).
- Once ANDA is approved, an applicant can manufacture and market generic drug to provide safe, effective and low cost alternative of innovator drug product to the public.
- Generic drugs are termed 'abbreviated' as they are not required to include preclinical and clinical data to establish safety and efficacy. They must scientifically demonstrate Bioequivalence to Innovator (brand name) drug.

- A generic drug is comparable to Innovator drug in dosage form, strength, route of administration, quality, performance and intended use.
- One of the ways to demonstrate bioequivalence is to measure the time taken by generic drug to reach bloodstream in 24-36 healthy volunteers. The time and amount of active ingredients in the bloodstream should be comparable to those of Innovator drug.
- Use of bioequivalence as base for approving generic drug products was established in 1984, also known as WAXMAN-HATCH ACT. It is because of this act that generic drugs are cheaper without conducting costly and duplicative clinical trials.

# INVESTIGATION OF MEDICINAL PRODUCTS DOSSIER (IMPD)

- The IMPD is the basis for approval of clinical trials by the competent in the EU.
- The Clinical Trial Directive came in force harmonizing the laws, regulations and administrative provisions of the Member states relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use.
- The directive introduced a harmonized procedure for the authorization to perform a clinical study in any one of the EU Member States.
- In addition, it defines the documentation to the documentation to be submitted to the Ethics Committee as well as the IMPD to be submitted to the competent authority for approval.

- Dossier; A collection of documents about a particular person, event or subject. E.g. Patient's medical record Medicinal product dossier; File containing detailed records about a particular drug product.
- **Objectives:** Since clinical trials will often be designed as multi center studies, potentially involving different Member States, it is the aim of this guideline to define harmonized requirements of the documentation to be submitted throughout the European Country.

## **GUIDANCE AND LEGAL BASIS**

- The following guideline is to be seen in connection with Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use, which came into force on June 20, 2014.
- Since clinical trials will often be designed as multi -centre studies, potentially involving different Member States, it is the aim of this guideline to define harmonized requirements for the documentation to be submitted throughout the European Union.
- It should be clearly differentiated between the requirements for a dossier for a clinical trial and a marketing authorization dossier.
- Information to be provided for investigational medicinal products (IMPs) should focus on the risk aspects and should consider the nature of the product, the state of development/clinical phase, patient population, nature and severity of the illness as well as type and duration of the clinical trial itself.

## SCOPE OF THE GUIDELINE

- This guideline addresses the documentation on the chemical and pharmaceutical quality of IMPs and Auxiliary Medicinal Products containing chemically defined drug substances to be submitted to the competent authority for approval prior to beginning a clinical trial in humans.
- IMPs based on innovative and complex technologies may need more detailed data to be submitted.
- For certain situations, e.g. where the drug substance from the specific source to be used for an IMP is already included in a medicinal product authorized within the EU, not all the documentation need to be submitted in the IMPD, but a simplified IMPD will sufficient

## **FULL IMPD AND SIMPLIFIED IMPD**

- When applying for a clinical trial authorization, a full IMPD is required when little or no information about an IMP has been previously submitted to competent authorities and/or when there is no MA in the Community.
- However, there are situations where a simplified IMPD will be sufficient. A simplified IMPD may be submitted if information has been assessed previously as part of a Marketing Authorization in any clinical trial to that competent authority.
- There are also situations where the SmPC of a Marketed Product will be sufficient as the IMPD. A SmPC may be submitted if the IMP has a Marketing Authorization in any EU Member state.

## **FULL IMPD CONTENTS**

- Data on drug substance.
- Basic data on clinical study.
- Clinical object.
- Manufacturing supply and import.
- Pre clinical data.
- Quality data.
- Non clinical pharmacology and toxicology data.

## **DATA ON DRUG SUBSTANCE**

- General information about drug like nomenclature, structure, general properties, composition.
- Manufacturing process and manufacturer name.
- Characterization.
- Packaging material used for the drug substance should be stated.
- For auxiliary medicinal products the same requirements and principles apply as for investigational medicinal products.

## **BASIC DATA ON CLINICAL STUDY**

- Cover letter, protocol, clinical trial summary.
- Content of medicinal product.
- Applicant's information.
- Duration of trial.
- Number and type of patient.
- Description of therapy and background.
- Mode of gene transfer.
- Origin of target cells.
- Dosing or treatment schedule.

## **MANUFACTURING, SUPPLY AND IMPORT**

- GMP facility description.
- Description of manufacturing process and process control.
- Evaluation of safety.
- Import license.
- This section should provide summaries of all available data from pre clinical trials and human experience with the proposed IMP.
- Dose information on pre clinical study.
- A statement of the Good Laboratory Practice (GLP) status and Good Clinical Practice (GCP) status should provide of all studies.

## QUALITY DATA

- If the IMP does not have a marketing authorization in the EU, but is manufactured in the EU, a copy of the manufacturing authorization certificate should be provided.
- If the IMP does not have a marketing authorization and is not manufactured in the EU, a copy of the certificate that the manufacturing complies with good manufacturing practices (GMP) by the qualified person should be provided.
- The sponsor should provide summaries of non clinical pharmacology and toxicology data for any IMP use in the clinical trial.
- If sponsor does not provide any data then he have to justify why he does not provide them.
- The data should provide in tabular form accompanied by the briefest narrative highlighting the main salient point.

# CHANGES AND AMENDMENTS TO THE IMPD

- Although the following list is not exhaustive, substantial changes to the IMPD are likely to be caused by changes concerning one or more of the following:
  - Importation of the medicinal product.
  - Change of name of IMP.
  - Packaging material.
  - Manufacturer(s) of drug substance.
  - Manufacturing process of the drug substance.
  - Specifications of active substance.
  - Specification (release or shelf-life) of the medicinal product.
  - Specification of excipient where these may affect product performance.
  - Major change to the formulation.
  - Storage conditions.
  - Test procedures of active substance.
  - Test procedures of the medicinal product.

# INVESTIGATOR'S BROCHURE

- The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.

## Purpose:

- Its purpose is to provide Information to the Investigators and others involved in the trial such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedure.
- The IB also provides insight to support the clinical management of the study subject during the course of the clinical trial.

- The information should be presented in a concise and simple manner.
- IB enables a clinician or potential investigator, to understand it and make his/her own unbiased risk benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB.
- **General Considerations:**
  - Title Page
  - Sponsor name
  - The identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor).
  - The release date.
  - Confidential statement

# Confidentiality Statement

- The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.
- The investigator brochure should include:
  1. Table of Contents
  2. Summary
  3. Introduction
  4. Description of IB
  5. Nonclinical Studies
  6. Effects in Humans
  7. Summary of Data and Guidance for the Investigator.

- **Summary:** A brief summary should be given highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information of the investigational product.
- **Introduction:** A brief introductory statement should be provided that contains
  - The chemical name (and generic and trade name(s) ) of the investigational product.
  - All active ingredients
  - The investigational product
  - Pharmacological class and its expected position within this class (e.g. advantages),
  - Therapeutic, or diagnostic indication.
  - The introductory statement should provide the general approach to be followed in evaluating the investigational product.

- Physical, Chemical, and Pharmaceutical Properties and Formulation.
- A description should be provided of the investigational product substance( the chemical and/or structural formula(e)), and brief summary should be given of the physical, chemical, and pharmaceutical properties.
- To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) used.
- Instructions for the storage and handling of the dosage form(s) should also be given.
- Any structural similarities to other known compounds should be mentioned. Nonclinical studies.
- Introduction: The results nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, possible unfavorable and unintended effects in humans.

# INDIAN GCP

- 1. Definitions
- 2. Pre-requisites for the study
  - 2.1 Investigational Pharmaceutical Product
  - 2.2 Pre-Clinical supporting data
  - 2.3 Protocol
  - 2.4. Ethical & Safety Considerations
- 3. Responsibilities
  - 3.1. Sponsor
  - 3.2. The Monitor
  - 3.3. Investigator
- 4. Record Keeping and Data Handling
  - 4.1. Documentation
  - 4.2. Corrections
  - 4.3. Electronic Data Processing
  - 4.4. Validation of Electronic Data Processing Systems
  - 4.5. Language
  - 4.6. Responsibility of Investigator
  - 4.7. Responsibilities of Sponsor and Monitor

- 5. Quality Assurance
- 6. Statistics
  - 6.1. Role of Biostatistician
  - 6.2. Study design
  - 6.3. Statistical Analysis
- 7. Special Concerns
  - 7.1. Clinical Trials of Vaccines
  - 7.2. Clinical Trials of contraceptives
  - 7.3. Clinical Trials with Surgical Procedures / Medical devices.
  - 7.4. Clinical Trials for Diagnostic agents – Use of radioactive materials and
  - 7.5. Clinical Trials of Herbal Remedies and Medicinal Plants
- 8. Appendices
  - Appendix I Declaration of Helsinki
  - Appendix II Schedule Y
  - Appendix III Format for submission of Pre- clinical and clinical data for r-DNA based vaccines, diagnostics and other biologicals.
  - Appendix IV Investigator's Brochure
  - Appendix V Essential Documents

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## **Purpose of I.B.**

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