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Preclinical Drug Development Program:

The journey towards submission of IND application

We are now supporting you through all the stages in a drug development continuum

Veeda Group

We provide technical expertise to bridge the gap between preclinical drug development and clinical trial phases. The IND-Enabling package of Veeda Group is designed to meet the needs of both pharmaceutical and biopharmaceutical companies. Services provided by Veeda Group help sponsor companies to submit and get IND approval for their Investigational new drug.

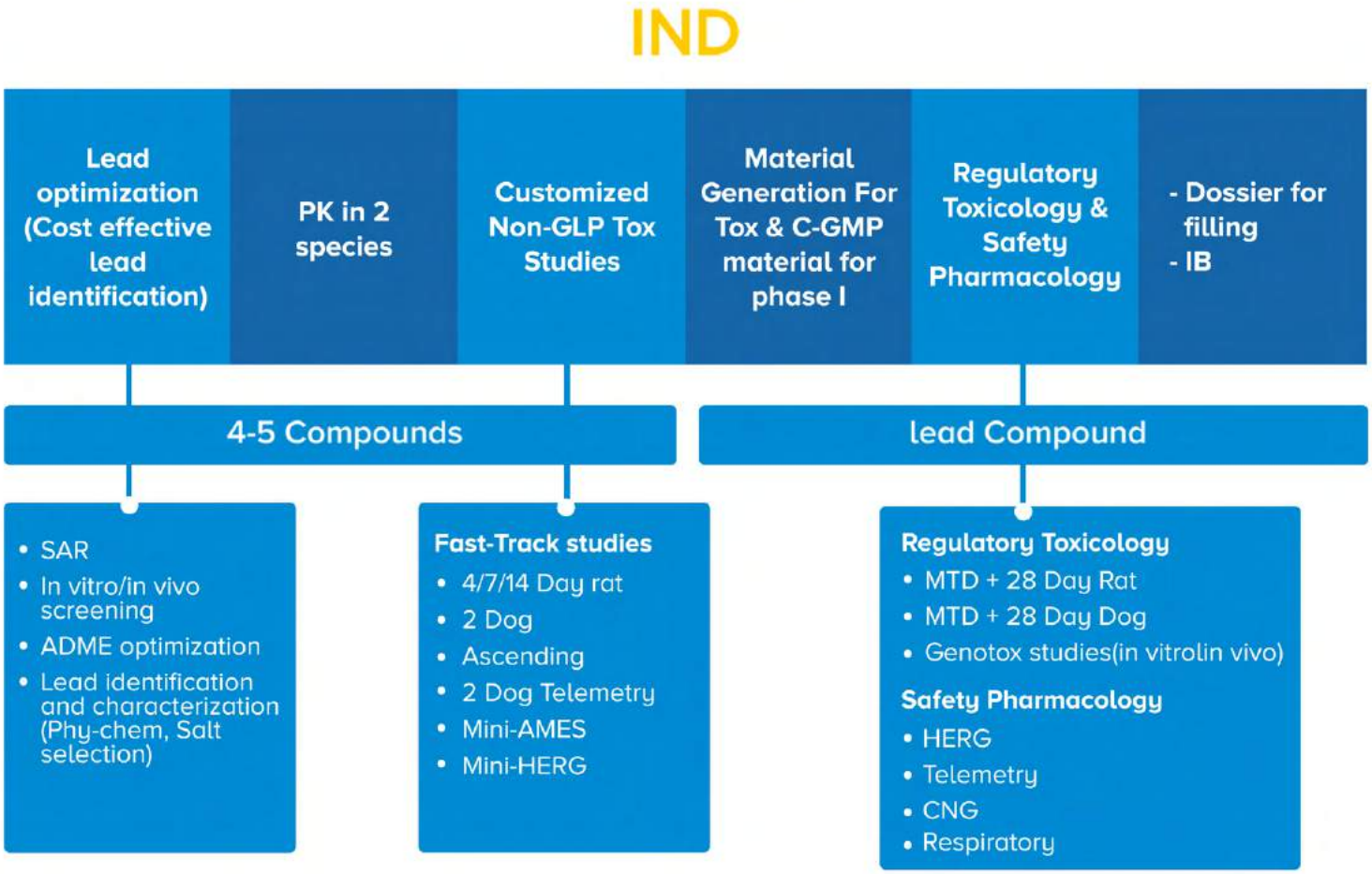

Figure 1. IND Enabling Services by Veeda Group

Karen L Steinmetz and Edward G Spack through their published article on preclinical drug development for neurodegenerative disease have mentioned in detail the different components of a preclinical drug development program. We here present a brief overview of that article. A preclinical drug development program for IND submission contains the following components:

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1. Target Product Profile

Target Product Profile (TPP) designs the framework, which is very useful to assess if the required goal of developing a new drug is met in every stage of its development cycle. It minimizes the risk of failure in new drug development to a great extent as it gradually evolves with the progress in the drug-development program.

The general content of a TPP document includes:

1. Market size, competition, and differentiators
2. Therapeutic indication/indications
3. Key trial endpoints
4. Expected clinical use
5. Target of the drug and its mechanism of action
6. Chemistry, Manufacturing, and Control (CMC) profile
7. Age range of patient
8. Bioavailability and duration of action
9. Dosage form, route of administration, and frequency of administration
10. Safety, precautions, and contraindications
11. Patent status and any modifier of exclusivity

2. Pharmacology and Experimental Toxicology

Before submitting an IND application, the sponsor needs to carry out the efficacy, pharmacology, and experimental toxicology studies in rodents and non-rodents. This is necessary to determine the safe dose, proper route, and frequency required for future studies which involve a human being. During the early developmental stage or preclinical stage, bioavailability and PK studies are conducted in vivo to determine the ADME characteristics of the drug. Initial dose range-finding and toxicity studies during preclinical trials are carried out to provide a rationale for setting dose levels in more complex definitive studies. Toxicity studies are carried out as per OECD guidelines. However, the major objective of toxicity studies and initial dose range-finding studies include:

- Determination of maximum tolerated dose (MTD)
- Identification of signs of toxicity

3. Active Pharmaceutical Ingredient (API)

Preclinical studies during drug development require an adequate supply of high-quality API to conduct GLP-toxicology and Non-GLP toxicology studies. Non-GLP toxicology studies include **efficacy studies, early formulation activities, and in vivo dose range-finding studies.**

APIs are manufactured by different processes such as chemical synthesis, fermentation, recombinant DNA or other biotechnology methods, according to ICH Q7 Good Manufacturing Practices

Some pharmaceutical companies prefer to outsource the synthetic process of API development to specialized CROs that will produce required batches along with a Certificate of Analysis or GMP release for each batch. The primary objective of outsourcing is to get a high-quality API batch ready to be used in GLP safety toxicology studies or prepared/formulated for clinical use.

4. Formulation

Once an NCE is discovered and identified as an API through preformulation studies, the next step is to convert that NCE into a suitable formulation through which preclinical studies can be carried out. Innovator companies carry out solubility studies, permeability studies, studies to improve oral bioavailability, excipient selection, salt form screening and characterization, and some other conventional and special studies on the API to prepare a suitable formulation to carry the drug development program with minimal animals. A suitable formulation has the following properties:

- **API is soluble in the solvent**
- **The excipients are non-toxic to the test animal**
- **The formulation is equally effective in a small volume considering the species involved in the study**

The preclinical formulations are administered by intravenous (for solutions) or peroral routes (includes suspensions). One must remember that preclinical studies are expensive, and appropriate decisions in choice and design of preclinical formulation prevent repeating the same research on animals and saves time and money.

To overcome these challenges in preclinical formulation, the sponsor company needs a preclinical formulator. Along with the help of an analytical scientist and pharmacokineticist, the preclinical formulator plays a vital role in the progression of the drug development program from the wet chemistry lab to the preclinical testing phase. The drug formulation should meet the primary objective of the preclinical study, which is to maximize exposure or efficacy by presenting the highest possible number of molecules of the NCE at the site of action.

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5. Analytical and Bioanalytical methods

Analytical methods are used to determine the purity and the quality of the formulation prepared for preclinical studies. Bioanalytical studies are carried out with an objective to assess the overall ADME characteristics of the experimental drug substance in the physiologic fluids of the test animal.

The analytical work consists of two components:

1. **R&D component (includes analytical method development and analytical support for preformulation and formulation)**
2. **GLP/GMP component**

During bioanalysis, final sample is prepared which is suitable and optimized for LC/MS MS analysis. Finally the estimation of total drug exposure is determined by the Area under the Curve (AUC). Special pharmacokinetic softwares and a non-compartment model provide a reliable estimation of total drug exposure.

The objectives to carry out analysis of the preclinical formulation include:

- **Verification of the active and inactive components**
- **Determining the presence of impurities**
- **Confirmation of dissolution properties**
- **Assessment of potency**
- **Determining the shelf-life stability**
- **Determining whether decomposition has occurred**

Key objectives for Bioanalysis include characterization of:

- **PK disposition in rodents and non-rodents (single dose, multiple dose, and absolute bioavailability)**
- **Route dependent PK disposition**
- **Definitive in vitro drug-drug interaction potential**
- **Toxicokinetics in toxicology species**
- **PK disposition of parent and metabolite in pharmacological and toxicological species**
- **In vivo drug-drug interaction studies**

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6. Pharmacokinetics, Toxicokinetics, and Metabolism

Pharmacokinetics determines the dose level and frequency of administration of the study drug. PK studies in animals elucidate the in vivo DMPK properties of the drug candidates. According to IND application requirements, PK studies are carried out in two species a) rodents and b) non-rodents. PK parameters of significant interest are peak plasma concentration (Cmax), the time of peak plasma concentration (Tmax), clearance, half-life, and especially bioavailability.

The pharmacokinetics and bioanalysis of experimental compounds involve time and money. Thus, sponsor companies outsource Formulation Analysis and PK analysis to experienced high-quality CROs to save time and money and get the best results in return for the drug development program.

Toxicokinetic studies help to understand the behavior of the study drug when given at maximum dose, the steady-state, and its accumulation in the body after repeated administration.

Metabolism studies are carried out using in vitro methods with the following objectives:

- Determine drug-drug interactions

Absorption
Permeability
- Caco-2 (A-B and B-A);
- PAMPA; MDCK-MDR-1

Solubility
- Aqueous (various pH)
- SGF and SIF*

Pharmacokinetics
- Mice; Rats; Rabbits
- Dogs and Monkeys (Partnered)

Distribution
Protein binding
- Equilibrium dialysis (ED)
- Ultra filtration
- ED method to determine fu in plasma and brain

X-Functional Activities
- PK-PD

Metabolism
- Liver microsomes; S-9
- Fractions and Hepatocytes

CYP and FMO profiling
- CYP inhibition

Metabolite ID
- In vitro using liver microsomes, hepatocytes
- In vivo from plasma, bile, urine and feces
- Glutathione trapping
- Blood/plasma partitioning
- Time dependent inhibition
- Plasma and Chemical stability

Excretion
- Mass balance (metabolic cages)
- Biliary and Urinary Excretion

7. Pivotal Toxicology and Safety

The primary method to assess the safety of a study drug during its early phase development is to carry out the single-dose and repeat dose toxicology studies involving rodent and non-rodent species. Along with the safety assessment, animal studies also help determine the candidate drug's no observable adverse effect level (NOAEL). The sponsor should carry out a minimum of two complete GLP compliant safety studies along the same route of administration as the proposed clinical route for IND-directed safety studies. One can understand more about the toxicokinetic and safety studies in animals by reading the ICH S2 (R1), S3, S7A, and S8 guidelines.

8. The final step is the pre IND meeting with the regulatory authority and later filing the IND

Filing an IND requires completion of 3 sets of forms:

FDA Form 1571: Detailing the study

FDA Form 1572: Providing information about the investigator and study site

FDA Form 3674: Certifying that the study is registered in the national database of clinical trials.

The contents of an IND application include:

1. Cover letter
2. FDA Form 1571
3. FDA Form 1572
4. Introduction
5. General Investigational Plan
6. Investigator's Brochure
7. Study Protocols
8. Chemistry and Manufacturing (CMC)
9. Pharmacology and Toxicology
10. Previous Human Experience with Investigational Agent
11. Additional Information
12. Bibliography

The journey from preclinical phase to Phase I trials in humans involves many complex stages. Get in contact with us at **www.veedacr.com** to meet our experts and get an end-to-end solution for getting IND approval of your study drug.

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