

Enough of Clinical...Let's talk Pre-Clinical!

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ABSTRACT

In drug development, pre-clinical development, also named preclinical studies and nonclinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data is collected. The main goals of pre-clinical studies are to determine the safe dose for First-in-man study and start to assess product's safety profile. Products may include new or iterated or like-kind medical devices, drugs, gene therapy solutions, etc. This paper talks about preclinical trials conducted in animals prior to testing in human subjects.

INTRODUCTION



Figure 1. Pre-Clinical testing

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

To meet FDA's requests, during preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. As a summary, the following data are needed to fulfill the requirements, including:

- ADME
- Acute Pharmacology

- Metabolic Stability
- Genomic Biomarker Analysis
- Protein Biomarkers
- CYP Screening
- Assay Metabolites
- Pharmacogenomics/Toxicogenomics
- In vitro Toxicity
- Mutagenicity
- In vivo Toxicity

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The three types of preclinical research are:

- In Vitro – In glass, as in a test tube. An in vitro test is one that is done in glass or plastic vessels in the laboratory
- In Silico – an individualized computer simulation used in the development or regulatory evaluation of a medicinal product, device, or intervention.
- In Vivo – In the living organism. For example, an experiment that is done in vivo is done in the body of a living organism.

FDA requires researchers to use good laboratory practices (GLP), defined in medical product development regulations, for preclinical laboratory studies. The GLP regulations are found in 21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies. These regulations set the minimum basic requirements for:

- study conduct
- personnel
- facilities
- equipment
- written protocols
- operating procedures
- study reports
- and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product

Preclinical research is a key step in the development of new disease treatments. Most frequently, a compound will only be tested in patients once it has been shown to be efficacious in an animal model that reliably reflects the human disease. Therefore, the choice of an appropriate animal model and the experimental parameters to assess the efficacy of a new chemical entity is crucial. Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug should be tested in people. Pre-clinical studies give a lot of useful information, but they don't give all the answers that are needed. After all, humans and mice can be very different in the way they absorb, process, and get rid of substances. A treatment that works against cancer in a mouse may or may not work in people. And there could be side effects and other problems that didn't show up when the treatment was used in mice. If the pre-clinical studies are completed and the treatment still seems promising, the U.S. Food and Drug Administration (FDA) must give permission to test it in humans.

PRECLINICAL DRUG DEVELOPMENT STAGES

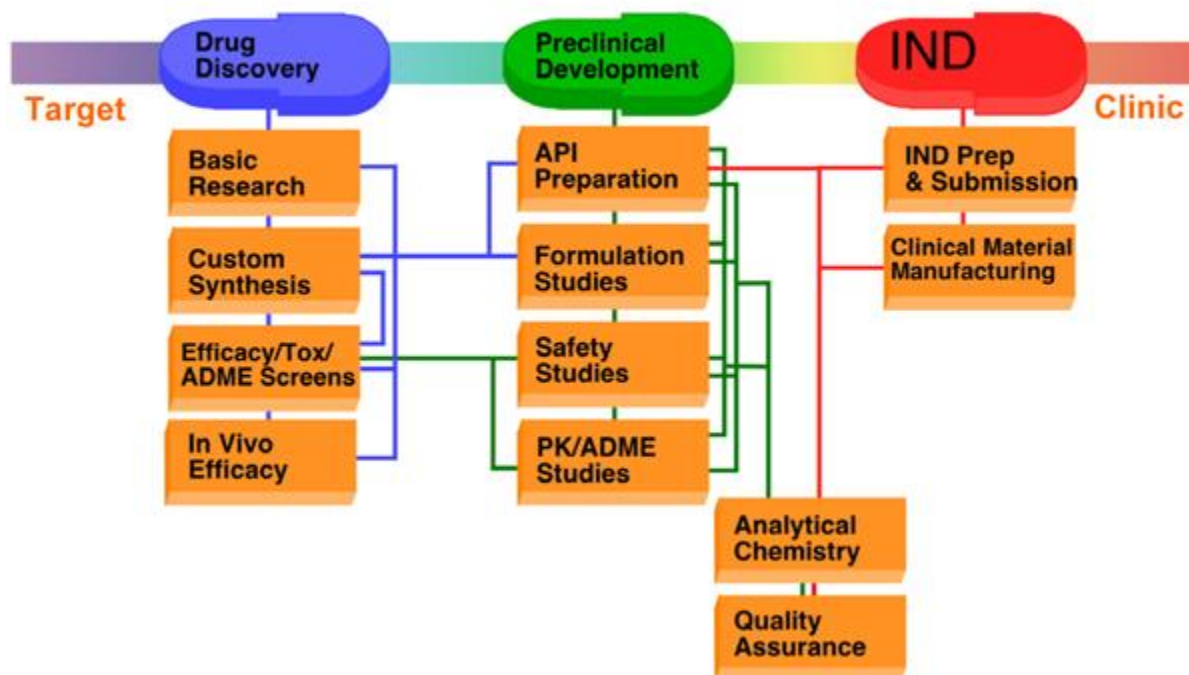


Figure 2. Preclinical Drug Development Stages

Following identification of a drug target and candidate compounds, several early activities, such as pharmacology, in vivo efficacy, and experimental toxicology, can contribute to the selection of a lead candidate for preclinical development. These preclinical activities provide the basis for an Investigational New Drug (IND) application to the FDA for permission to initiate clinical testing in humans.

ANIMAL TESTING

The information collected from these studies is vital so that safe human testing can begin. Typically, in drug development studies animal testing involves two species. The most commonly used models are murine and canine, although primate and porcine are also used.

CHOICE OF SPECIES

The choice of species is based on which will give the best correlation to human trials. Differences in the gut, enzyme activity, circulatory system, or other considerations make certain models more appropriate based on the dosage form, site of activity, or noxious metabolites. For example, canines may not be good models for solid oral dosage forms because the characteristic carnivore intestine is underdeveloped compared to the omnivores, and gastric emptying rates are increased. Also, rodents can not act as models for antibiotic drugs because the resulting alteration to their intestinal flora causes significant adverse effects. Depending on a drug's functional groups, it may be metabolized in similar or different ways between species, which will affect both efficacy and toxicology.

Medical device studies also use this basic premise. Most studies are performed in larger species such as dogs, pigs and sheep which allow for testing in a similar sized model as that of a human. In addition, some species are used for similarity in specific organs or organ system physiology (swine for dermatological and coronary stent studies; goats for mammary implant studies; dogs for gastric and cancer studies; etc.).

ETHICAL ISSUES

Animal testing in the research-based pharmaceutical industry has been reduced in recent years both for ethical and cost reasons. However, most research will still involve animal based testing for the need of similarity in anatomy and physiology that is required for diverse product development.

ANIMAL CARE FACILITIES

(a) A testing facility shall have a sufficient number of animal rooms or areas, as needed, to assure proper: (1) Separation of species or test systems, (2) isolation of individual projects, (3) quarantine of animals, and (4) routine or specialized housing of animals.

(b) A testing facility shall have a number of animal rooms or areas separate from those described in paragraph (a) to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

(c) Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

(d) When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.

ANIMAL SUPPLY FACILITIES

There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.

ANIMAL CARE

(a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals.

(b) All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice.

(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

(d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification. All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit.

(e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.

(f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.

(g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

(h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.

(i) If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.

NO OBSERVABLE SIDE EFFECTS

Based on pre-clinical trials, No Observable Adverse Effect Levels (NOAEL) on drugs are established, which are used to determine initial phase 1 clinical trial dosage levels on a mass API per mass patient basis. Generally a 1/100 uncertainty factor or "safety margin" is included to account for interspecies (1/10) and inter-individual (1/10) differences.

CONCLUSION

Once a single promising compound is selected based on the kinds of basic research and therapeutic, companies initiate preclinical studies both in vitro and in animals to evaluate a drug's safety and potential toxicity. These preclinical studies are also used to assess potential effectiveness. Sponsors design additional studies to provide convincing evidence that a drug is not mutagenic (i.e., it does not cause genetic alterations) or teratogenic (i.e., it does not cause fetal malformations). Because a patient's ability to excrete a drug can be just as important as the patient's ability to absorb the drug, other preclinical studies focus in detail on those factors.

REFERENCES

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