The Importance of Early-Stage Development

By: Devan Patel, Senior Director, Project Management

To avoid the risks, costs, and possible pitfalls that typically terminate projects during later stages of drug development, it's important for companies early-stage development the time and respect it deserves. This is an especially critical piece of advice for smaller pharma firms that have less capital to spend on R&D and may be tempted to minimize the budget for research solutions during early-stage development.[1]

Both large and small pharma and biopharma organizations can mitigate risks and costs by partnering with a contract development and manufacturing organization (CDMO) that specializes in early-stage development processes, including pre-formulation studies and drug product evaluations, to quickly get to a go/no-go decision, scale up formulations from lab to IND, and accelerate timelines in the post-IND stage.

Pre-Clinical Studies

The adage "begin with the end in mind" is particularly appropriate for pre-clinical development, as the resulting IND must support the planned clinical trial design. Pre-clinical development encompasses the activities that link drug discovery in the laboratory to initiation of human clinical trials. Pre-clinical studies can be designed to identify a lead candidate from several hits; develop the best procedure for new drug scale-up; select the best formulation; determine the route, frequency, and duration of exposure; and ultimately support the intended clinical trial design.[2] Pre-clinical studies involve defining safety characteristics, pre-formulation studies, drug product evaluation, CMC planning, and clinical trial design.

Define safety characteristics

Industry experts cite the most important element of the pre-clinical process is selecting the best new molecular entities to enter into the clinical trials and to limit failure in full development. Thus, the priority during the preclinical selection process lies in the safety and efficacy testing of a new molecular entity.

According to Regulatory Professionals consultants, the first step in evaluating a new chemical entity (NCE) or new molecular entity is conducting *in vitro* and *in vivo* preclinical studies that define relevant safety characteristics.[3]

These include:

• **Safety pharmacology** studies to assess how the drug affects the respiratory, cardiovascular, and central nervous systems, among others

• **Pharmacodynamics studies** to establish the drug's mechanism of action and contribute to dose selection for clinical studies

• **Toxicology studies** to determine much drug can be safely administered and how frequently, including the maximum tolerated dose; the no-observed-adverse-effect level, which determines the first-in-human dosage; and whether repeat doses are toxic

• **Pharmacokinetics assays** to characterize how the drug is absorbed, distributed, metabolized, and excreted

Pre-formulation Studies

Life science leaders describe pre-formulation studies as the process of "learning before doing." These laboratory studies determine the characteristics of an active pharmaceutical ingredient (API) and excipients that may influence formulation and process design and performance.

These studies include:

- Solubility
- API Stability
- pH Stability
- Physicochemical properties of the API
- Excipient Compatibility
- Component Compatibility (for generics not NCEs)
- Particle Size Testing

Drug Product Evaluations

During pre-clinical drug development, the drug's toxic and pharmacological effects need to be evaluated through *in vitro* and *in vivo* laboratory animal testing. The Food and Drug Administration (FDA) requires sponsoring companies to develop a

pharmacological profile, determine toxicity in at least two species of animals and conduct short-term toxicity studies.[4] The following steps will be taken during drug production evaluation:

• Solubility studies for improving dissolution, bioavailability and concentration of API in toxicology dosage form;
• Preparation of simple concentrated dosage forms for animal toxicology dose ranging studies (API in bottle, powder in bottle, solutions, suspensions);
• IND enabling pre-clinical dosage form development-minimizing API use;
• Phase-appropriate method development/verification for formulated drug product;
• Formulation and prototype screening and testing;
• Stability of formulation/dosage form;
• Lyophilization cycle development/optimization if needed
• Cleaning method development/validation.

Clinical Trial Design

Clinical trial design is the final step of the pre-clinical phase. Scientists determine the appropriate amount of the drug to achieve both safety and efficacy through microdose, single ascending dose, or multiple ascending dose trials. For randomized trials, decisions must be made on the type of blinding. Will the new entity be tested against an approved comparator or placebo? Supplemental safety studies may also be required at one or more phases.[3]

When the trial design has been finalized, an investigational new drug (IND) or analogous clinical trial application, must be filed with the FDA, the European Medicines Agency, and/or the regulatory bodies of any other countries where you are planning to conduct the study. This application requests authorization to administer the biopharmaceutical to humans. Requesting a pre-IND meeting with the agency prior to submission may be useful for resolving questions, addressing concerns, and preventing surprises right before your trial is set to start. The FDA requires a briefing package with relevant materials and data at least a month before a requested meeting.[3]

Clinical Development

Pre-clinical work goes hand in hand with Phase I/II clinical development. The Biotechnology Innovation Organization of clinical success rates in advancing drugs to market between 2006 and 2015 found that only 9.6% of drugs entering Phase I clinical testing will reach the market, and following phases II 30.7% of drugs fail.[5] A CDMO will create a seamless transition from pre-clinical formulations to Phase I/early Phase II clinical supplies to help ensure a program’s success.

During the early stages of clinical development, the investigational focus is on safety monitoring:[3]

• Phase I studies typically evaluate safety in a small number of healthy volunteers. Preliminary efficacy assessments in affected patients may be included in Phase I, if the therapy is being evaluated in patients and is intended to address an unmet or life-threatening medical need.

• Phase II trials aim to determine whether the drug is safe and effective in a larger cohort of patients with the condition being treated. After this stage, an end-of-Phase II meeting with the FDA should be scheduled to review pivotal (Phase III) trial design. Close interaction with the FDA, including a meeting to prepare for submission of an Investigational New Drug application, is critical to ensure that the preclinical development package properly supports the planned Phase I clinical trial.[2]

About Pii

Pharmaceutics International, Inc. (Pii) is a CDMO that specializes in early-stage development. Pii has experience across wide array of molecules, including BCS II-IV, potent/containment products, poorly soluble drugs, as well as environmental and manufacturing controls for handling early stage compounds with limited available toxicology data.

About the Author

Devan Patel is the Senior Director, Project Management at Pharmaceutics International, Inc (Pii).

Devan has held roles of increasing responsibility in Project Management leading key development and commercial programs for Pii for both the orals and injectables. With his leadership, Pii has built a world-class Project Management Organization (PMO) consistently characterized by a superb customer experience. Over the years, Devan has used his knowledge and technical skills to play a vital role for the Operations team, managing key initiatives for the Parenteral/Sterile business unit, including managing the overall scheduling and planning of all Aseptic Operations. His collaborative style when working with cross-functional teams across Pii's business units and ability to anticipate problems before they occur as raised the role of project management to an art form. Devan delivers a positive, outcomes-focused experience for our client-partners, from initial contact through successful completion of each project.

Devan earned his Bachelors in Cell Biology and Molecular Genetics from the University of Maryland and an M.B.A. from Johns Hopkins University.

References

1. Avoiding Pitfalls and Costly Mistakes in Early Stage R&D, Shawn Hooks, *Pharma R&D*, Jan. 17, 2017.
2. The basics of preclinical drug development for neurodegenerative disease indications, *BMC Neurol*. 2009; 9(Suppl 1): S2.
3. Product Development Checklist: Considerations for Each Stage of the Drug Development Process, Regulatory Professionals, April 6, 2021.
4. Preclinical Studies Definition, SPINE-Health.
5. Phase II Trials in Drug Development and Adaptive Trial Design, *JACC Basic Transl Sci*. 2019 Jun; 4(3): 428–437.