Crystal Pharmatech
Suite 500-B, 3000 Eastpark Blvd
Cranbury, New Jersey 08512, USA

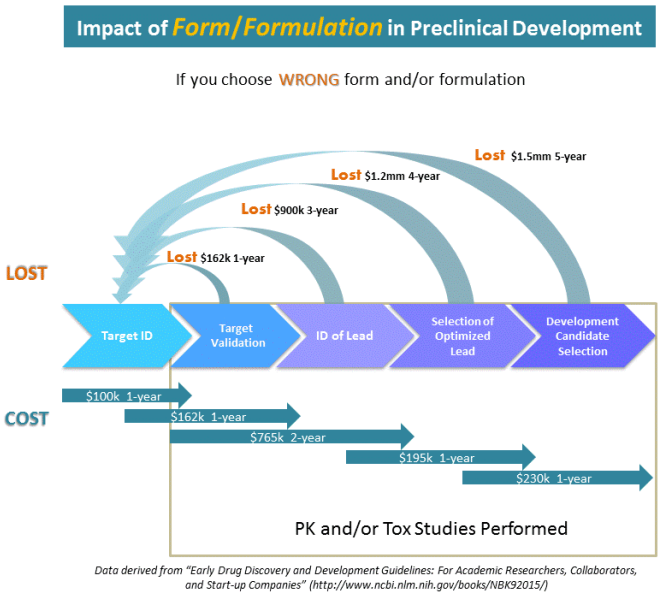
www.crystalpharmatech.com
info@crystalpharmatech.com
1-609-529-4135

Optimal Preclinical Formulation Development

Integrating the efforts of drug-discovery scientists, material scientists and formulation specialists earlier in the discovery process can reduce drug-development timelines, risk and overall costs and provide other competitive advantages.

The ability to streamline and improve any pre-clinical development effort will have direct, strategic business implications for the drug-development team, as well. Specifically, return on investment will come from the ability to:

- Shorten timelines associated with the clinical program (and therefore potentially shorter time to market).
- Maximize earnings potential, revenue, profit margin and market share (by receiving regulatory approval sooner).
- Minimize competition in some cases (for instance, by receiving market exclusivity and other benefits if the product is first to market for a given indication).
- Eliminate unnecessary experiments and PK studies by using a more focused approach.
- Reduce the number of animals required for toxicology studies.
- Reduce overall risk associated with the drug-discovery and commercialization program.



Data derived from "Early Drug Discovery and Development Guidelines: For Academic Researchers, Collaborators, and Start-up Companies" (http://www.ncbi.nlm.nih.gov/books/NBK92015/)

When material scientists and formulation specialists work closely with developmental scientists early in the process, they can use lab-based techniques, simulation and modeling to evaluate the options and select the optimal way to administer the target molecule, in terms of how best to put the drug into solution and keep it in solution (in terms of optimized form and the use of appropriate excipients) and how best to administer that formulation into the body (to maximize exposure to the blood stream). By narrowing the choice of form and formulation options *before* the initiation of animal-based testing, researchers can help to isolate and reduce avoidable variability, so that the testing data truly reflect the inherent variability of the compound itself, in terms of metabolism, excretion and so on — and not just variability that may be the result of too many other "moving parts." Adjustments in study design that are made as a result of these early efforts, before the initiation of animal-based toxicology studies — which is the case when using a trial-and-error approach — will have less schedule or budget impact.

The improved approach discussed here aims to incorporate the costly lessons and wisdom learned, to help drug developers carry out their drug-development programs with greater depth of knowledge, and use it to

realize shorter overall timelines — and help reduce risk and cost.

Using a tiered approach provides a good way to make the appropriate investments needed to blend preclinical drug-development and solid-state research efforts for each stage of development.

For instance, lab-based investigation can be tiered, according at the following stages of discovery and development. These efforts can be timed and scaled on a case-by-case basis, to stagger the investment, depending on such factors as the required timetable, the amount of available compound and so on:

• **Developability 0** — *Studies to understand solid-state material properties and formulation requirements, and use that information to screen lead candidate properties and flag potential risks*. The goal is to understand how solid-state properties (such as solubility) will impact the selection of the most suitable vehicle for a single-dose pharmacokinetic study in a preclinical species, and support related formulation activities for early safety and PK assessment.

•**Developability 1**—*Physicochemical -characterization studies to support multi-day, multiple-dose animal studies in various species*. The goal is to fine-tune dose-selection and dose-limiting toxicology studies that are needed to identify the maximum feasible dose, MFD).

• **Developability 2**— *Studies to finalize full-scale phase screening and final selection, and refine the formulation as needed*. The goal is to enable GLP safety and toxicology studies that are needed to support the IND filing, and identify the most appropriate formulation that can be used with human patients in later clinical trials.

• **Developability 3**— *Studies to align the readiness of the drug substance and drug product in order to meet clinical study requirements and ensure a timely filing of the IND and FIH start*. To goal is to guide the formulators on the selection of the most suitable excipients, assuming that an oral dosage form will be used (based on the FIH-enabling studies) .

While drug-development efforts also require a blend of art and science. The approach discussed here aims to impart 'more science and less art,' and has been shown to deliver better results and realize shorter timelines for all of the key developmental milestones.

Summary

- Neglecting the impact of API form in early preclinical formulation can lead to significant cost and time penalties.
- Do the right amount of work at the right time – use a staged approach.
- Understand risks with API form and formulation during every stage of development.
- Integrate needs and desires of formulators, process chemists and engineers.

References

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