Complete preformulation toolkit protects pipeline assets

The-drug development process can be lengthy and costly. On average only one out of 5–10 thousand compounds evaluated in early discovery globally, becomes a marketable drug costing at a cost approximately $1 billion over 10-15 years. [1]

To meet this challenge, scientists need a thorough evaluation before selecting a candidate to progress. A candidate selection without due diligence can increase costs dramatically and timelines can be impeded by setbacks such as insufficient dose for toxicity studies or in the ability to formulate a patient acceptable dosage form. A solution can be found through a complete preformulation evaluation, including animal PK studies, to help ensure that a new chemical entity (NCE) can reach its desired target and potential bioavailability challenges are mitigated. In this article, we will explore how innovators can reduce delays and overcome issues so they can advance a candidate to IND with confidence.

Preformulation bridges discovery data with development goals. WuXi STA's IND Enabling Preformulation Package (IEPP) is an integrated Pre-CMC package for small molecules, oligonucleotides, and peptides. IEPP uses a range of in vitro, in vivo, and in silico tools to determine a compound's fundamental properties and determine the expected pharmacokinetics and bioavailability. In vitro tools and early analytical tests including early stability-indicating studies inform formulation scientists and enable a physical form selection that fits the drug product form and patient requirements.

Compound characterization and profiling

Understanding solid-state properties of an NCE plays a crucial role when developing dosage forms. A comprehensive data set including Tm, pKa & LogP/D, solubility, permeability, dissolution, super-saturation, physical form, and chemical stability are evaluated at the onset of the preformulation investigation. This data set is used extensively in the solid form selection, and for oral dosage forms, an indication of potential bioavailability limiting factors.

Solid form selection

Solid form selection is a pivotal decision that can impact later stage formulation options. Our search for the ideal solid form starts with salt and polymorph screening, most appropriate for finding a crystalline form. However, molecules with solubility challenges often need advanced screening that includes exploring co-crystals and amorphous solid dispersion (ASD).

Bioavailability

In the case of oral drugs, the compounds must dissolve in the intestinal tract to be absorbed into the bloodstream. Therefore, the solubility of a compound is an important parameter for drug candidate selection and should be taken into consideration during preformulation to ensure feasible formulation development. Unfortunately, a staggering 70% of pipeline drugs are classified as poorly soluble – falling under either BCS Class II or BCS Class IV – and therefore have poor oral bioavailability [2].

IEPP's solution uses a panel of enabling technologies to find the best option to increase the compound's solubility. Two popular examples are spray drying and hot melt extrusion, which converts drugs into an amorphous state by distributing the API throughout a polymer network, thus creating an amorphous solid dispersion. Spray-dried dispersion (SDD) is a popular technique for fast animal PK and toxicology dosing as well as its compatibility with later stage dose forms through scalable technology that can be applied from preclinical through to commercial scale with minimal process rework for scale-up.

Alternative enabling techniques such as micronization and nanosuspension can also be used, which decrease the size of solid drug particles, subsequently increasing the surface area and enhancing the drug's dissolution rate.

For high lipophilic compound, lipid based micro-emulsion could be another approach to attain the drug substance solubilized in the GI fluid and absorbed.

In addition to potential solubility issues the drug's permeability must then be assessed. We use a set of in vitro tools such as PAMPA, Caco-2, and MDCK to better predict permeability, and assess the relative contributions of active transporters in membranes in the permeation process.

Conducting comprehensive preclinical work and optimizing formulations as early as possible mitigates the risk of compounds failing later in development, saving time and lowering development costs.

In silico prediction with animal PK

Our pre-formulation package includes rapid animal PK studies. These quick tests, often done in at least two species, require only 1-2 weeks and less than 1 g of the NCE.

Armed with the solubility, permeability, dissolution, and animal PK data, we use modeling and simulation software to predict in vivo absorption profiles in different species, including humans. We can assess with different parameters, such as particle size, pH level, dose range to simulate different gastric environments to inform toxicologists and clinicians for dosing specifications.

Stability

Stability studies are also integral and should be performed during candidate selection. Data to support the formulation remains within acceptable chemical and physical limits for the planned study duration is required. With IEPP a compound's physical and chemical stability, as well as its photostability, are all assessed in solution and solid-state conditions, typically through the use of forced degradations studies. This data enables the toxicity studies and informs for the first in human.

Accelerated timelines

Proper characterization of your drug candidate gives it the best chance of making it to the market. However, some innovators adopt a trial-and-error approach for candidate selection as they are eager to accelerate their candidate into development. Unfortunately, this can backfire, often requiring the discovery team to start the selection process over, which ultimately drives up costs and further delays timelines. We understand the need to move quickly and bring therapies to patients fast so our optimized IEPP program delivers all the required data for even challenging NCEs within weeks. Compounds that fall into the DCS I and III categories can be complete in as few as 6 weeks, with only 2 g of API. When the data reveals a bioavailability challenge, (DCS II and IV), we screen the compound through our broad enabling technologies to identify the best solution. The additional time required to find the suitable formulation, only 6 additional weeks on average, is a fraction of failing a toxicity trial or even worse, failing First in Human. (*See Chart 1*)

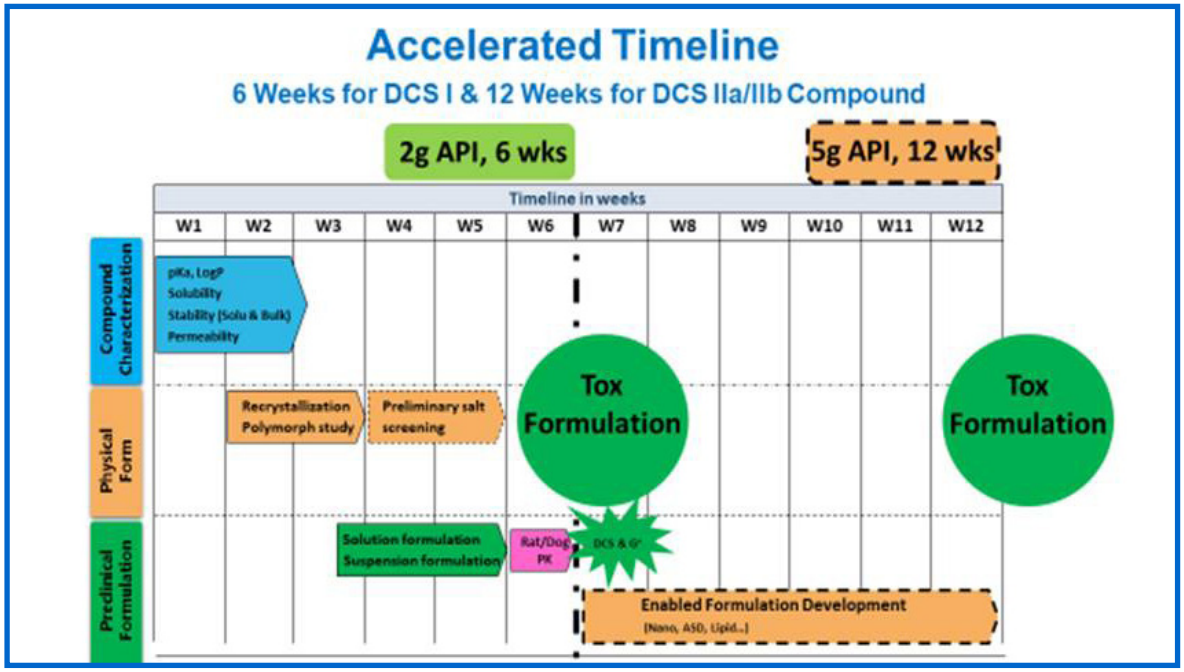

Chart 1: IEPP Timeline Candidate Selection to GLP Tox

When outsourcing pharmaceutical development work, it is pivotal that innovators select a CDMO that can offer an end-to-end service including both in vitro and animal PK preclinical work paired with advanced enabling technology screening. WuXi STA's integrated approach combines efficient high-quality drug substance development and manufacturing together with the drug product expertise. The DS-DP integration avoids any delays waiting for API production or time lost for material or knowledge sharing. The streamlined approach allows innovators to advance candidates with a better chance of clinical success in significantly shorter timeframes and subsequently with a lower overall cost.

1. (https://www.researchgate.net/publication/341097009_The_Stages_of_Drug_Discovery_and_Development_Process)

2. https://www.americanpharmaceuticalreview.com/Featured-Articles/135982-The-Innovator-Pipeline-Bioavailability-Challenges-and-Advanced-Oral-Drug-Delivery-Opportunities/