Formulation Development

Introduction

WuXi AppTec provides a comprehensive set of services for vehicle screening in early discovery and formulation design and optimization for late discovery. The services include standalone in vivo or in vitro assays for API and formulation characterization or an integrated package designed to identify and optimize a formulation to support various animal studies at different drug discovery stages, such as early pharmacokinetic (PK) screening, preclinical proof-of-concept studies, efficacy and early toxicological assessment. A summary of the various formulation studies offered in WuXi are listed in Table 1 (in vitro) and Table 2 (in vivo). The in vitro studies can also be referenced in the Physicochemical Property Measurement chapter of this catalog. Based on the clients’ needs, WuXi DMPK works closely with WuXi’s Pharmaceutical Development Services (PDS) to plan out a specific formulation screening and development strategy according to compound availability, required dose schedule, delivery route, pharmacological model and stage of development.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Description</th>
<th>Deliverables</th>
<th>TAT (working days)</th>
<th>Weekly Capacity (CMPDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Characterization</td>
<td>- Physical characterization of raw API as received (PLM, XRPD, TGA and DSC)</td>
<td>• Physical property parameters</td>
<td>3</td>
<td>As needed</td>
</tr>
<tr>
<td>HPLC</td>
<td>• HPLC method development and simple qualification for API assays on solubility and stability studies</td>
<td>• Analytical method</td>
<td>10</td>
<td>As needed</td>
</tr>
<tr>
<td>Chemical Stability</td>
<td>• Buffer stability (pH 2.0, 4.0, 7.4, 9.0)</td>
<td>• %Remaining</td>
<td>5</td>
<td>As needed</td>
</tr>
<tr>
<td>Initial Vehicle Screening</td>
<td>• Vehicle decision tree development based on availability and quality of compound, tolerability of the vehicle in the selected animal model and development possibilities • Simple solubility test in different vehicles • Fast formulation screening approach for early discovery PK screening</td>
<td>• Visual description or photograph of vehicle screening at different concentrations • Dose analysis of final vehicle</td>
<td>0.5-1</td>
<td>40 formulations/week</td>
</tr>
<tr>
<td>Formulation Screening</td>
<td>• Partial physicochemical characterization (pKa, log D, Sw) • Formal solubility test (equilibrium solubility) of compound in different excipients • Suspension characterization with homogeneity, particle sizing and solubility measurement • 7-day RT or 4°C stability evaluation for final formulation • PK study evaluation for lead formulations • Formal formulation development for late discovery PK, PK/PD, MTD and non-GLP pre-tox</td>
<td>• pKa, log D, aqueous solubility profiles (optional) • Solubility results from different vehicles • Microscopy (with photograph) for coarse particle size evaluation • PK profile and PK parameters</td>
<td>As needed</td>
<td>As needed</td>
</tr>
<tr>
<td>Nanosuspension</td>
<td>• Suspend poorly water soluble compounds in various vehicles and physically grind them to decrease the particle size to a nanodispersion</td>
<td>• D90&lt;1µm</td>
<td>10</td>
<td>As needed</td>
</tr>
<tr>
<td>Development of an ASD Formulation</td>
<td>• Prepare and evaluate ASD formulations with different polymers/surfactants at various ratios • Examine physical stability, solubility and recommend 1-2 leading ASDs</td>
<td>• Significantly improve solubility of API in aqueous media</td>
<td>10 or more</td>
<td>As needed</td>
</tr>
</tbody>
</table>

Table 1. In vitro studies to assist in early stage discovery formulation development.
Studies for Developing a Formulation

Solubilization Technology

WuXi has a broad set of solubilization techniques to support discovery formulation screening and development. Techniques are selected based on project need, API and formulation characteristics which include:

- pH adjustment
- co-solvents
- surfactants
- complexation
- particle size reduction
  - lipids/emulsions
  - salt form
  - solid dispersions
  - nanosuspension
  - combinations

<table>
<thead>
<tr>
<th>Assay</th>
<th>Description</th>
<th>Species</th>
<th>Deliverables</th>
<th>TAT (working days)</th>
<th>Weekly Capacity (CMPDS)</th>
</tr>
</thead>
</table>
| Biopharmaceutical Evaluation Study 1 | • IV or PO administration of compound via a parallel or crossover single dose  
  • IV administration of a clear solution and PO administration of free form and/or several salt forms  
  • Pretreatment with an acid modifier (pentagastrin, HCl or famotidine) before dosing  
  • Blood samples collected at specific time points  
  • n=3/group | - Rat  
  - Dog  
  - NHP | • PK profiles  
  • PK parameters | As needed | As needed |
| Biopharmaceutical Evaluation Study 2 | • PO administration via a parallel or crossover single dose  
  • Administration of a clear solution as a reference and suspension with different dose levels  
  • Capsule, tablet or other dosage forms can be evaluated  
  • Pretreatment with an acid modifier (pentagastrin, HCl or famotidine) before dosing  
  • Blood samples are collected at specific time points  
  • n=3/group | - Rat  
  - Dog  
  - NHP | • PK profiles  
  • PK parameters  
  • Ratio of dose to exposure | As needed | As needed |
| Food Effect Study            | • PO administration of compound in pre/postprandial states  
  • Pretreatment with an acid modifier (pentagastrin, HCl or famotidine) before dosing  
  • Blood samples are collected at specific time points  
  • n=3/group | - Dog  
  - NHP | • Ratio of exposures | As needed | As needed |
| Animal Bioequivalence Study  | • PO administration of compound with reference and test formulations  
  • Pretreatment with an acid modifier (pentagastrin, HCl or famotidine) before dosing  
  • Blood samples are collected at specific time points  
  • n≥4/group | - Dog  
  - NHP | • Ratio of exposures | As needed | As needed |

Table 2. In vivo studies to assist in early or late stage formulation development.
**Vehicle Screening**

WuXi DMPK provides a fast vehicle screening service for early PK screening and preclinical proof-of-concept studies. The purpose of vehicle screening is to identify a simple aqueous and organic based solution with low compound requirements and a rapid turnaround time. For a typical screening PK study (IV+PO), the turnaround time is 5 working days and the DMPK formulation group is able to identify a standard vehicle for the PK study within 1 working day after receiving the test compound. Solubilization technologies such as pH adjustment and co-solvents are commonly used for vehicle screening. Combination approaches such as co-solvents plus surfactant or complexing agent plus pH adjustment are also considered for more challenging compounds. In addition, a decision tree is used for vehicle screening which is based on dose regimen, dose route and the impact of excipients on pharmacological endpoints for each project.

**Formulation Screening**

WuXi DMPK also provides a thorough formulation screen for later preclinical definitive PK studies for IND fillings, efficacy and preliminary toxicology studies. This approach consists of three steps. First is the selection of solubilization technologies and excipients based on a comprehensive understanding of the physicochemical properties (such as pKa, log D/log P and aqueous solubility) of each specific API. Second is screening the selected excipients to find the best fit formulation for the API by *in vitro* solubility assessment, homogeneity and particle size analysis. Lastly is the evaluation of the formulation candidates that promise to deliver the best bioavailability for *in vivo* PK assessment.

**Biopharmaceutical Evaluation**

As compounds move through development toward clinical testing, a step-wise evaluation of a compound's behavior in the GI track including oral absorption will be evaluated in animals. WuXi DMPK provides biopharmaceutical evaluation services in both rodents and large animals (dogs and NHPs). Animals are pretreated with an acid modifier to control the pH levels and gastric emptying time to better understand the impact on oral absorption. As shown in Table 1, there are two study types of biopharmaceutical evaluation. The first study assesses if absorption is dissolution rate limited for different API forms. The second study assesses if the compound exhibits solubility limited absorption. For this, suspensions, capsules, tablets or other dosage forms can be evaluated. These two studies are very helpful in defining further formulation development strategies.

**Food Effect Study**

Regulatory agencies recommend food-effect bioavailability (BA) studies for orally administered drug products as part of IND and NDA filings to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. Beagles are most commonly used to evaluate the exposure of a compound after being administered under preprandial or postprandial conditions which can positively or negatively influence absorption by various means including; delaying gastric emptying, stimulating bile flow and increasing lipid uptake, changing the gastrointestinal (GI) pH, increasing splanchnic blood flow, altering the luminal metabolism or efflux of a drug substance or physically or chemically interacting with a dosage form of the drug substance.

**Animal Bioequivalence Study**

Animal bioequivalence (BE) studies establish whether two formulations or batches of a drug produce the same plasma concentrations which will ultimately lead to the same therapeutic effects. These studies are typically conducted in animals before moving into humans before filing an abbreviated NDA (ANDA) for a generic formulation or biosimilar. Crossover study designs are preferable for the BE study. Two sequences of crossover doses with a washout period in between are applied to

**Case Studies**

**Case study I: oral formulation screening (DMPK Unit)**

A study was conducted to identify an appropriate formulation for the lead compounds for exploratory toxicity in rats. The study was composed of four phases including; vehicle screening, suspension assessment, chemical stability and PK evaluation of the selected formulations. For the vehicle screening phase, 16 test media were selected according to the test article's physicochemical properties, then the equilibrium solubility of the test compound was evaluated in each medium by HPLC or LC-MS. Based on the solubility results, a solution couldn't be achieved at the desired high dose concentration, so a suspension was considered and the study progressed into the 2nd phase, suspension assessment. In this phase, particle size
and suspension homogeneity were analyzed via microscopy (Figure 1) accompanied with HPLC or LC-MS. In phase III, the 7-day chemical stability was evaluated at room temperature for the final formulation using HPLC or LC-MS and the final formulation was then dosed to animals for PK assessment in phase IV. The PK result showed the final formulation delivered the desired bioavailability for lead compounds A and B and the AUC data had little variation among the animals (Figure 2).

Case study II: biopharmaceutical evaluation (DMPK Unit)

A study was conducted to evaluate the pH effects on the oral bioavailability of a test compound. The study was designed as a crossover with three phases. The animals in phase I and phase III were pretreated with famotidine and in phase II were pretreated with pentagastrin. The results indicate the compound exhibited dissolution rate limited absorption in the GI track and the elevated acid condition of the GI environment could enhance the oral absorption of the compound compared with the more alkaline GI environment (Figure 4).

Case study III: ASD formulation development to improve API aqueous solubility (Pharmaceutical Development Service Unit)

Amorphous solid dispersions (ASDs) of poorly water soluble or crystalline compounds were prepared with selected polymers at various ratios via the rapid solvent evaporation method. Prepared ASDs were tested for solid state characteristics and drug loading. The available ASDs were assessed for solubility in pH 6.8 buffer at 25°C and the solubility results indicate the ASD formulations can significantly improve API solubility compared to the crystalline API as shown in Figure 4.