Lead Optimization to Candidate Selection

Identifying a suitable phase and formulation to maximize exposures in preclinical species involves understanding the physicochemical properties of the compound. Phase optimization is not required at this stage. However, any change in phase can have a major impact on the formulation and the exposure multiples obtained.

At this early stage of pharmaceutical development, the key goal is a successful single dose PK study. One should not completely overlook solid state properties since the solid form and particle attributes of the API can impact dissolution, solubility, stability, and potentially bioavailability. One must identify a stable phase for single dose PK studies and a formulation for maximum exposure with acceptable stability. Key properties of the API that should be understood include:

- Crystallinity
- Melting point or Glass Transition Temperature (T_g)
- Particle Size
- Solid Form as delivered and at time of dosing
- Log D
- pKa
- Solubility in biorelevant media
- Solubility and stability in PK formulations
- Hygroscopicity or hydration/dehydration conditions

Choosing the appropriate PK vehicle should never be a “hunt and peck” approach. In order to ensure continuity, one must apply a SMART approach. If it is determined that dissolution is limiting your exposures, one can attempt some of the following approaches:

- Particle Size
- Salts
- Cocrystals
- Use of wetting agents
- Amorphous modification

If your compound is solubility limited, perhaps some of these options should be attempted:

- Solubilizing agents
- Cosolvents
- Micellization
- Complexation

The goal with respect to API solid form at this stage is a physical form that has the best absorption properties to provide for high exposure and good safety margins. The physical and chemical stability of the selected form must be evaluated to ensure that now form change will occur during the course of the animal studies.

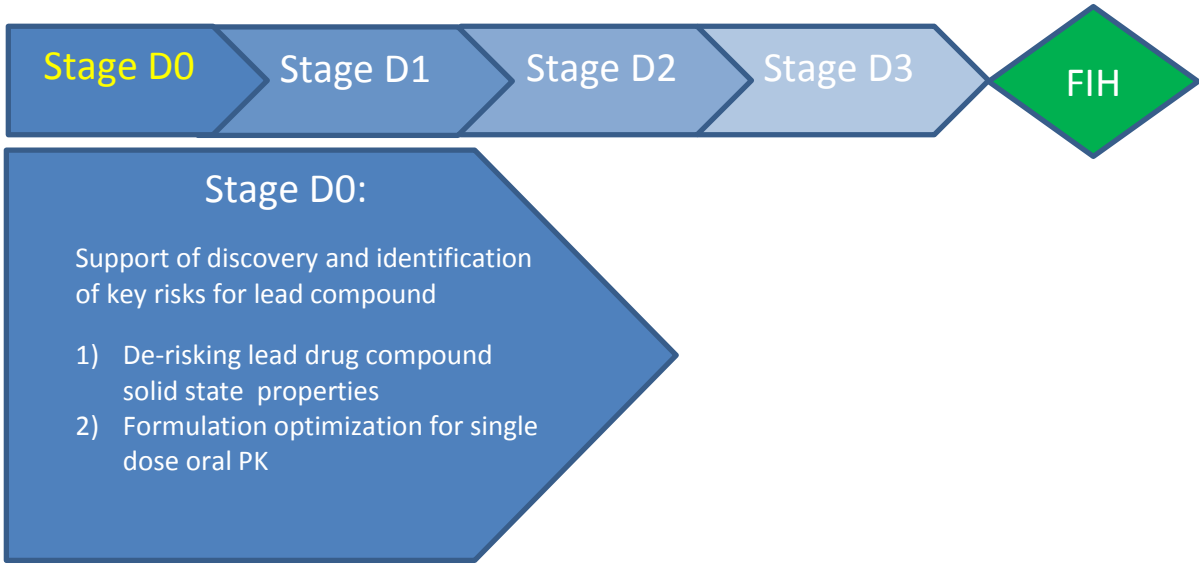
Some of the questions that need to be answered with sound fundamental research are:

- Is the dosing solution or suspension physically stable
- Is the API chemically stable in the dosing vehicle
- What is the solubility and stability in simulated biological fluids

At Crystal Pharmatech, we will design a suitable API phase and formulation to maximize exposures in preclinical species. Understanding the physicochemical properties of the compound is critical to help guide the formulation selection.

Summary

- Solid state properties really do matter in this early stage of development.
- Right work at the right time – don't front load work.
- Make sure you know the properties of API (Form/PSD/solubility) that you are dosing in animals.



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