An Executive Summary

From Bench to Clinic: Preclinical and First-in-Human Development Strategies

Pingyun (P.Y.) Chen, PhD
Director of Early Development
Catalent Pharma Solutions

Nathan Barksdale
Small Molecules and Peptides Scientist
Catalent San Diego

Crucial and cost-effective factors to consider when transforming a preclinical development compound into a first-in-human, early-phase drug candidate.

Overview

Drug developers must consider many factors when positioning a pre-clinical drug candidate to succeed in first-in-human clinical trials. This executive summary will map out the pre-formulation studies needed to create the best development path for a drug candidate and describe oral and injectable clinical formulation options for short- and long-term success.

Molecule Characterization

It costs more than a billion dollars and takes over a decade to advance potential drug candidate molecules from the discovery to a commercial drug product. The main reason is the very high attrition rate due to the lack of efficacy and safety. Thus, the right balance of time and resources must be spent on API synthesis, pre-formulation, pharmacokinetics, and animal toxicity studies, formulation development, and clinical material supplies.

The first step for a new molecule moving out of the discovery phase is the pre-formulation studies, or developability assessment. Indeed, pre-formulation work lays the foundation for choosing the right salt and polymorph, delivery technology, and formulation strategies. Key factors to evaluate and consider include:

- Solubility at different pH levels and in bio-relevant media,
- Dissolution behavior,
- Stability in solution- and solid-state,
- Partition coefficient,
- Ionization constant,
- Solid-state properties including salts and polymorphs, melting point, moisture absorption profile, bulk density, and flow properties.

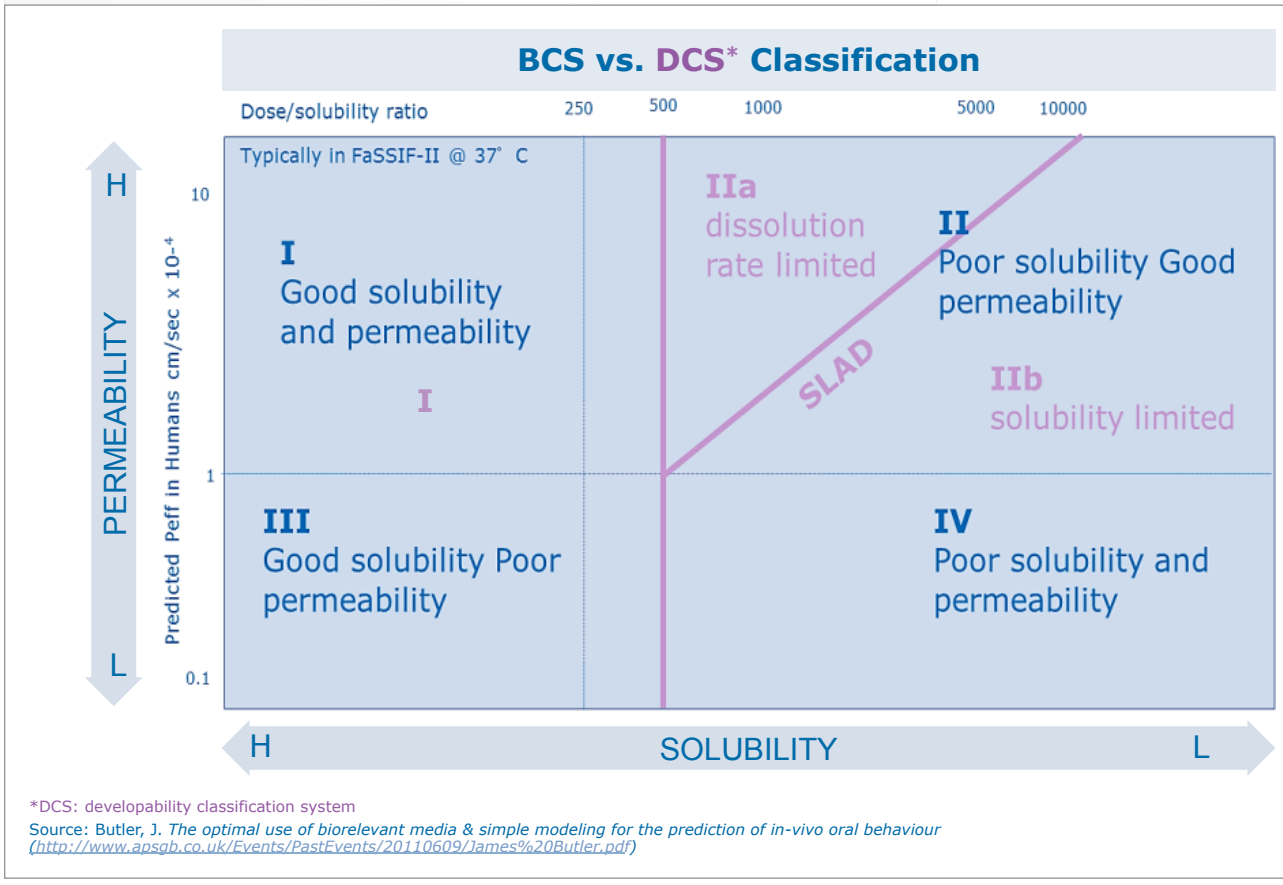
These data are used to assess the molecule's oral bioavailability and to guide formulation development. Scientists often use FDA's Biopharmaceutics Classification System (BCS) or Developability Classification System (DCS), both of which categorize molecules into four classes based on solubility and permeability (see **Figure 1**).

SPONSORED BY

Catalent

Pharmaceutical Technology

Figure 1: Biopharmaceutical Classification System (BCS).



*DCS: developability classification system

Source: Butler, J. *The optimal use of biorelevant media & simple modeling for the prediction of in-vivo oral behaviour* (http://www.apsgb.co.uk/Events/PastEvents/20110609/James%20Butler.pdf)

More than 90% of small-molecule drug candidates are poorly soluble and belong to DCS II or IV. Challenges with poorly soluble compounds include non-linear dose proportionality, variable pharmacokinetic (PK) data, and limited tox coverage. All of these may compromise human dosing prediction and studies. For these molecules, bio-enhancing formulations are required to achieve the desired toxicological coverage, consistent and good exposure (e.g., >30% bioavailability) in different animal species and humans.

Salt and Polymorph Selection

Salt formation is an effective way to modify the solubility of molecules with ionizable functional groups. More than half of all small-molecule drugs on the market are developed as salt forms.

For example, Eli Lilly's Zyprexa® (olanzapine) for schizophrenia was developed with several delivery methods using the free acid and different salt forms to achieve the necessary pharmacokinetic profile. The drug maker developed an orally disintegrating tablet (Zydis®) that can be taken without water, a combination product using the hydrochloride salt, and an extended-release injectable suspension using the poorly soluble pamoate salt, which allows the molecule to dissolve and release slowly over several weeks.

Salt and polymorph selection can also be used to improve a compound's physical properties, to enhance the API isolation and purification, and to improve the chemical stability of a particular molecule. All these changes are tied to the drug's overall performance, bioavailability, efficacy, safety, and shelf life. It is critical to consider all of these factors in the context of a compound's overall development plan and commercialization.

Oral Formulation Strategies: From Preclinical to Clinical Toxicity Studies

It is necessary to find a preclinical formulation for good laboratory practice (GLP) toxicity that provides the maximum exposure to hit the safety targets while being as simple as possible. Also, consider using the same lot of API as the planned first-in-human studies. Although this criterion is not mandatory if the compound is physically representative (e.g., the same form, similar morphology, and similar particle size), performing some type of in-use stability study is useful.

Preclinical formulation differs from first-in-human or clinical formulation. In preclinical studies, a higher linear exposure range is needed, well above the dosing limit intended to be used in humans. This will help get passed the no observed adverse effect level and the maximum tolerated dose.

In addition, the solubilizing agent may change going from screening molecules during the discovery phase into preclinical and then clinical formulations. The goal is to optimize the molecule's solubility and physiochemical stability to have a non-toxic, safe formulation that can be used for 28-day studies and beyond. Establishing GLP product manufacturing, if needed, and analytical support at this stage is also key.

From preclinical formulation to Phase 1, a drug product should be optimized for in-human testing. By Phase 2 trials, the formulation should be close to the final dosage form needed for the study population and for commercial manufacturing. The analytical factors to consider when going into Phase 1 human trials include placebos, taste, equipment, dosing flexibility, corporate value, limitations based on the compound's BCS classification, time, cost, and the compound's advantages and disadvantages.

In general, when choosing among three types of oral formulations and an injectable formulation, key factors to consider are the compound's BCS classification, the physiochemical characteristics, the amount of API available, and the resources needed to invest in formulation development.

Dosing Options for Testing Oral Formulations

When working with oral formulations, developers can consider several Phase I options that may help accelerate the introduction of a drug into clinical trials (see **Figures 2** and **3**).

Powder-in-Bottle (PIB). One approach is PIB, which typically progresses a molecule quickly (i.e., within one to four weeks) into the clinic at a relatively low cost, because a minimal amount of development and GMP manufacturing support is required. Analytical requirements for PIB are generally minor and the clinical dosing is very flexible.

For clinical presentation, the API can be shipped in bulk to the clinical site and the staff can then prepare the suspension or solution by dispensing the required amount of API and preparing the suspension or solution with a commercially available vehicle. PIB can be made into a solution at the clinic by mixing the API with a diluent like water or juice. Alternatively, the API can be pre-weighed in bottles at a CDMO prior to shipment. When finalizing your clinical dosing strategy, you should consider the stability of your suspended or dissolved PIB presentation, and the capabilities of the clinical site to determine whether single dose or multi-dose bottles will be more effective.

Additional consideration should be given to the aqueous solubility, the ability to create a true solution, or a uniform and reconstitutable suspension. Chemical stability and suspension uniformity will help determine the dosing time window and if multi-dose bottles are acceptable. One additional disadvantage of a PIB is that for BSC II and IV compounds, this approach offers few options in terms of solubility enhancement.

Finally, matching color and taste can be especially challenging in placebo-controlled trials.

Powder-in-Capsule (PIC). As with a PIB, the major advantage of a PIC is the postponement of advanced formulation development to save time and money. Unlike a PIB, a PIC can eliminate taste and patient compliance issues related to taste. The test methods are still relatively simple, except that a capsule shell disintegration or dissolution method must be developed and tested. Another advantage is that the PIC has a finished, sophisticated look resembling a final dosage form. The typical development timeline is shorter than a formulated unit since the development time and material requirements are minimal. However, particularly low or high strengths will require manufacturing at a CDMO rather than at the clinical site.

In general, the analytical requirements for a PIC are greater than for a PIB because you must account for the capsule shell. Disintegration and dissolution methods must be determined.

For the clinic, capsule sizes are typically limited to the range of size 4 to size 00. The simplest approach is to ship the API to the clinical site and have the staff fill the capsule as needed. Alternatively, the capsules can be hand-filled, semi-automated, or even automatically filled at a CDMO. If the dose range is less than 5 mg, specialty equipment may be necessary to fill the capsules. Finally, if the dose is greater than 500 mg, multiple capsules per dose may be needed.

Factors to consider include API solubility in aqueous environments and whether the API, when exposed to biorelevant

Figure 2: Oral dosing options.

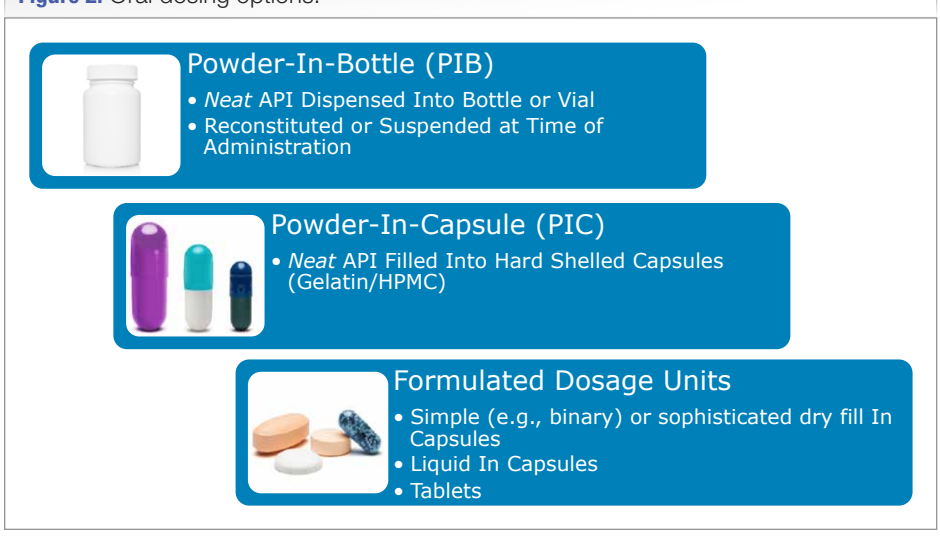


Figure 3: Options for testing drug formulations.

Consideration	Solution/ Suspension (PIB)	Neat API in Capsule (PIC)	Formulated Dosage Unit	Injectable
Analytical Requirements	API Stability In-use Stability	Assay, Disintegration Capsule Compatibility	Assay/RS, Disso, + Prototype Stability	Extensive
Placebos	Not Necessarily Trivial	Not an Issue	Not an Issue	Not Necessarily Trivial
Taste	Concern	Not an Issue	Not an Issue	N/A
Equipment Compatibility	Low Concern (high-shear mixing, low dose?)	Low Concern (unless low dose)	Critical (formulation expertise needed)	Critical (formulation expertise needed)
Clinical Dosing Flexibility	Very Flexible (suspension uniformity?)	Less Flexibility (usually 2-3 strengths)	Less flexibility Usually 3 strengths	Flexible
Corporate Value	Quick to Clinic	Quick to Clinic	Longer Lead Time/Cost Long-Term Value	Longer Lead Time/Cost Long-Term Value
Compound Characteristics	BCS I = Straightforward BCS II = Possible BCS III-IV = ?	BCS I = Straightforward BCS II-IV = ?	BCS I = Straightforward BCS II = Easier BCS III/IV = Better Chance	Soluble and Permeable Compounds = straightforward Poorly Soluble and Poorly Permeable Compounds = more challenging
Development Time	1-4 weeks	1-2 weeks	1-3 months	3-6 months
Relative Cost	$	$-$$	$$-$$$	$$-$$$

media, tends to gel. Disintegration can often be an issue for poorly soluble compounds when they are packaged as a PIC. For these compounds, simple blends with fillers and disintegrates will likely give better *in-vivo* performance. While the PIC process often works well for BCS class I and some BSC class II (or DSC IIa) compounds, it has limited utility for Class III and IV compounds since solubility and absorption aides cannot be include with formulation development.

Formulated Dosage Units. If a compound's solubility or bioavailability must be improved to achieve acceptable clinical profiles, a final option for oral dosing are formulated dosage units. This approach will generate a more sophisticated study that more closely represents the final, longer shelf life dosage unit used for later clinical trials. This approach also creates a faster transition to Phases 2 and 3 clinical trials. Depending on the complexity of the formulation, the development time can be one to three months. Overall, even though the lead time is longer and upfront cost is higher, long-term value is built in along the way, resulting in a higher corporate value, provided the compound advances passed Phase 1.

Typically, compounds with poor bioavailability require this route rather than a PIB or PIC. Using a formulated dosage unit—either a tablet or capsule, modified-release or liquid-filled—will also add early value to the drug development program, increasing the product's performance and stability. Such an approach may be more attractive to a big pharmaceutical partner or can increase the value of the asset when partnering.

The formulated dosage unit approach requires longer upfront development. More extensive excipient compatibility studies and process development are necessary; representative API in relatively large quantities will be needed. Prototype stability data to support an IND filing are necessary, as are more complicated drug product test methods for both release and stability that can be qualified. Assay-related substance methods that are specific to the formulation and established specificity with all the new components are also required, along with developing a dissolution method. With these requirements, excipient compatibility is critical, especially if an amorphous form is needed to enhance bioavailability.

As with PIC, placebos and taste-masking are generally not an issue, as it is relatively easy to make a matching capsule or tablet with a formulated dosage form. Also, dosing is less flexible than a PIB approach. The formulated units for BCS class I compounds are relatively straightforward, with simple blends and simple fills or direct compression. For BCS class II compounds, many options are available for bioavailability enhancement through dissolution rate and solubility enhancement. But for class III or IV compounds, there is a better chance of success compared to the PIC or PIB method since permeability enhancers may be included in the formulation.

With a formulated unit, the advantages of this approach include a better handle on shelf life and stability, a better developed placebo, and taste masking. Disadvantages include potential upfront work, added time, and extra cost, but a hidden advantage is that creating a very sophisticated technical package may be appealing to a partner or a big pharmaceutical company.

Injectable Formulation

Developers may want to consider using an injectable formulation for first-in-human studies if the compound has poor permeability, if they are dosing a small peptide, if there is enzymatic degradation, or if the compound has a heavy first-pass effect.

The benefits of an injectable formulation include excellent control of exposure and dosing, as well as the ability to use depots or target deliveries. Conversely, the analytical requirements are extensive in terms of stability, extractability, leachability, sterility, endotoxins, and particulate testing. Additionally, the development time is much longer and the costs are also much higher due to sterility requirements. Another issue to consider is drug-to-equipment compatibility, making early selection of a fill–finish site paramount. For example, extractables and leachables testing is highly depended on the fill–finish site's manufacturing materials.

The long-term value of this formulation approach is that once the first-in-human formulation is developed, it can be used with minor modifications for later stage clinical trials. This formulation type is relatively straightforward for soluble and permeable compounds; however, for poorly soluble and poorly permeable compounds, it can be challenging to meet the level of solubility in aqueous media to allow for injectable dosing.

Conclusion

Thorough pre-formulation studies and formulation development are necessary investments in the long-term clinical success of potential drug compound. Detailed preclinical characterizations such as salt selection, polymorph screening, and the "drugability" of a compound, as well as the evaluation of different delivery technologies and formulations for a timely and cost-efficient transition from preclinical to clinical drug candidate studies are crucial. In choosing the formulation type to develop, corporate factors must be considered such as the time and resources. Scientific considerations, time, cost, quality, and corporate commitment to the asset must be considered when selecting the best strategy for your compound and your company's needs.