



Essential aspects to consider when transitioning a lead candidate from Drug Substance to Drug Product using enabling formulation strategies.



Introduction

As part of our small molecule insights interview series, we review the Essential aspects to consider when transitioning a lead candidate from drug substance (DS) to drug product (DP) using enabling formulation strategies". This interview with Dr David Pearson (Director of Form and Formulation) from Sygnature Discovery Ltd aims to establish the important factors for consideration and challenges outsourcers may face when selecting enabling strategies to overcome physicochemical limitations of the DS prior to clinical evaluation. This article aims to support outsourcers with considerations for service provider selection and identify what value service providers can add as part of the overall project team.

After a short period as a medicinal chemist, David transitioned into this area of science 20+ years ago leveraging structural insights into the day to day work to help move molecules out of the lab and into the clinic and patients in need.

A highly experienced solid form subject matter expert with extensive expertise at the interface of medicinal chemistry, process chemistry, DMPK, and pharmacology. Supporting clients rapidly advance their molecules from the laboratory to the clinic, by understanding, controlling, and optimising solid state properties such as crystallinity, stability, and dissolution and delivering robust processes that transfer seamlessly into cGMP production.

Understanding the lead candidate:

1. How do you assess physicochemical liabilities such as solubility, permeability, chemical stability, and polymorphism?

Sygnature is a full service offering CRO and, as such, we work closely with our colleagues in in-vivo and DMPK to understand a molecules liability that are hindering its progression. If its solubility or permeation, we can develop formulations to address those. Close collaboration between solid-form scientists and formulation teams enables a thorough understanding, control, and purposeful modification of solid-state properties within the same laboratory environment.

2. What is your process for evaluating developability risk early (e.g., BCS classification, PK optimization, manufacturability)?

We typically engage with programs as they advance into in-vivo studies. Whilst the in-life teams are experienced at developing low concentration formulations (e.g. 1mg/ml), projects requiring high dose PK or toxicity studies often encounter challenges such as non-linear exposure or poor tolerability on repeat dosing. In these situations, reformulation is necessary to meet the needs of the projects. A formulation suitable for a high dose PK study is unlikely tolerated for a repeat dose toxicity study. Data from these studies can then help refine the predicted human dose, at which point a more aggressive



enabling formulation may no longer be required. Through rapid DMT cycles, we can perform early clinical formulation development and de-risk the selection of the most appropriate technology for First in Human studies, followed by technology transfer when necessary.

3. What pre-formulation studies do you consider essential before selecting an appropriate enabling strategy?

At an early stage, we need to understand the physical form of the material that generated early data. Was it crystalline or was it amorphous? It's not uncommon for amorphous material to show 10X solubility vs crystalline material. We then start to look at the structure. Does it have functionality suitable for salting? Does it have a high logP where lipidic formulations might help? What's the T_g of the neat API?

4. How do you incorporate early ADME/PK data into formulation decision-making?

This is critical, and where a multi-disciplinary team turns into a scientific powerhouse for a client. Numerous times we hear and see the confusion where people equate solubility with bioavailability. For a fair percentage of cases, they might be correct, but if there are permeation issues, efflux issues or first pass metabolism liabilities, increasing solubility targeting hepatic absorption might not solve the problem. Only by understanding the root cause, can you perform the correct experiments that will overcome those issues.



A multi-disciplinary team turns into a scientific powerhouse for a client

Dosage Form Design Considerations (Pre-clinical/Clinical)

5. Which enabling technologies do you routinely use (e.g., amorphous dispersions, lipid-based formulations, nanoparticles, salts/co-crystals)?

We pride ourselves in using the most appropriate technique for the challenge to hand. We do not force a square peg into a round hole because we have a round hole to fill. We have, in house, spray drying, lyophilisation, milling and lipidic formulation platforms to enhance the performance of the material. If the solid state properties aren't suitable for a particular technology, we adapt and can modify those with salt and co-crystal screens so that, for example, we raise the T_g to make an ASD more stable, to provide a material with a morphology suitable for nano-milling, or sufficient thermal stability for hot melt extrusion.

6. What are your preferred *in vitro* screening techniques when evaluating formulation performance and discrimination between prototypes prior to embarking on *in vivo* studies.

Developing a formulation for *in vivo* studies requires more than preparing compound in a vial that has good properties. **What matters is how that formulation performs** once dosed, and this is where Sygnature focuses. Our process begins with a two-stage dissolution assessment designed to mirror the physiology of the species of interest, acknowledging parameters such as dosing volume, gastric capacity, pH, and transit times, as these vary widely between species. For lipidic formulations, digestion studies are run to understand how excipient breakdown by lipases may influence exposure. For amorphous solid dispersions (ASD), we design bespoke dosing media to ensure smooth and reproducible gavage while still preserving the performance characteristics. Each of these steps helps us build a clear picture of how a formulation will behave *in-vivo*.





7. How do you decide between competing formulation options when the science is ambiguous?

Ordinarily, when we have two or three formulations within the same technology class and the in vitro data cannot discriminate between them, the only option is often to take multiple candidates in vivo with the Sygnature team. However, we work hard to avoid unnecessary in vivo work wherever possible, mindful of the 3Rs. In addition to dissolution, we can also assess flux across a PAMPA membrane to further triage formulations. Additional considerations also guide our decision making: ease of dosing, excipient tolerability, cost, and both physical and chemical stability for long term studies. For late-stage formulations, we start to think about how easy this could translate to a human. **While dosing liquids via gavage may be preferable in pre clinical species, a human drug product will be different.**

We therefore consider early on whether a given formulation could translate to a suitable human dosage form, such as compatibility with a soft gelatine shell, dose size, ease of manufacturing etc.

8. What criteria do you use to ensure translational relevance from preclinical formulation to clinical formulation?

Many pre clinical formulations are designed to boost the performance of the material and generate the exposure needed to support decision making. This data is used by our DMPK colleagues, through PBPK modelling, to predict the human dose. This predicted dose to man allows us to assess which formulation technologies are most appropriate for progressing the drug substance into a drug product. If only a modest improvement in dissolution rate is required, a particle size control strategy may be sufficient; if enhanced supersaturation is needed to enhance C_{max} and shorten T_{max}, an ASD may

be appropriate. If first pass metabolism is hindering development, and the molecule possesses the right physicochemical attributes, a lipidic formulation can be used to enhance lymphatic uptake and bypass hepatic clearance.

Our ability to move rapidly through the DMT cycle, optimising formulations across multiple parameters, enables us to efficiently progress a product toward development and can then be transferred into a GMP environment, with confidence on manufacturability, performance, stability and thus helping bring new medicines to patients in need.

Application of Theory

9. In your experience:

A. What is your typical timeline from lead candidate selection (DS) to clinical formulation lockdown?

If we have followed the molecule for discovery to candidate nomination, and the PBPK modelling now gives us a dose to man, a realistic DMT cycle for clinical formulations can range from a few months with a strong data package, to a year, depending on the complexity. Some formulations are naturally slow to produce and test (e.g. lyophilisation's) whereas some are very quick (e.g. lipidic) but they both carry the need for optimisation, stress testing such as ICH stability, excipient compatibility and finally a technology transfer to a GMP environment.

B. Can you breakdown the steps involved and the critical decision points that are assessed during this critical period of development?

Locking down the drug substance is one of the first things we focus on. We need to understand whether the material is crystalline (preferred form) or amorphous, and whether we're working with the free form, a salt, or a co crystal. Choosing the most stable



polymorphic form early on helps avoid issues later, especially as the program moves forward and the input crystal form may change. And while the route of administration is usually oral, that's not always the case; we regularly work on IV, subcutaneous, inhaled, and intranasal routes, so it's important to confirm this upfront. Once we know the form of the material, the intended route, and the expected dose, we can start drafting a Target Product Profile and use that to guide the development path.

10. What enabling formulation challenges have you solved, and how?

This is a long list. For example, we worked with a client whose Phase I formulation was a lyophilised powder, 150 mg split across three vials for infusion. The safety profile was so good the dose increased to 600 mg. Since using twelve vials per dose simply wasn't practical, we reformulated the product into a liquid concentrate which, given its moderate aqueous solubility, was a genuine challenge.

Another example, a client needed to slow down their dissolution to reduce clinical side effects. By carefully selecting polymers, we were able to create a product that achieved exactly that. We also have numerous examples from pre clinical programmes where our form and formulation expertise has transformed amorphous APIs by crystallising them and then developing formulations that delivered linear PK profiles up to 500 mg/kg. The same API was later reformulated for a 28 day tox study, providing the required exposure without any formulation related adverse effects.

We frequently use SMEDDS and SNEDDS to enhance bioavailability as well. Demonstrating lymphatic uptake is never straightforward, but when you see a five fold increase in bioavailability, the data often speaks for itself.

11. How early do you aim to identify the “clinical-intended” formulation, and how often does it change later?

Clinic ready is our goal, we are designing medicines for humans not rodents. With a rapid DMT cycle in a fully equipped lab, we can de-risk formulations and optimise rapidly in a non-GMP environment without the need for CAPA's, change orders and paperwork where multiple signatures are required before work can resume. Our quality, speed and flexibility help move a molecule out the lab and into the clinic.



At Sygnature Discovery, we create exceptional scientific outcomes. For our customers, who bring life-changing medicines to patients; and for our people, who help make this possible.

We're 700+ scientists from over 50 countries, working as one across Europe and North America. With no competing internal programs, we offer total confidentiality and commitment.

Over the past 20 years, we've earned a track record of real impact: 60+ advanced candidates, 200+ patents filed, 200+ active projects. Over 90% of our customers choose to stay with us – from biotechs racing to clinic to pharma companies that need specialised expertise for targeted challenges.

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