FAQs: Integrated Preformulation Studies for Fast Advancement of Drug Candidates to Human Clinical Studies

The cost and time required to develop a new drug are significant, and increase when drugs fail due to inadequate physicochemical and biopharmaceutical attributes, unacceptable safety, and sub-marginal efficacy. In a *PharmTech* webcast on, "Integrated Preformulation Studies for Fast Advancements of Drug Candidates to Human Clinical Studies," Liang Mao, director of developability and formulation research at WuXi STA, and Andrew Phimister, CMC Consultant, Seaview Pharma, spoke about how development attrition rate can be reduced. Here, they answer several audience questions from the webcast.

When should I start thinking about developability and solubility issues for my compound?

Phimister: The sooner the better, but you have to balance several factors such as financial resources and material availability. Ideally once good solution PK or efficacy data is observed, then a preliminary assessment of physical form (crystalline or amorphous), solubility, and chemical stability are performed. As a lead progresses and confidence grows to the point that it will be the likely development candidate, then it is important to fully profile the material and determine the most suitable clinical dosage form. If there are multiple candidates, then a streamlined testing protocol can be developed to focus on the most relevant challenges for a program or scaffold at an early stage (e.g., poor solubility). A small upfront investment can save a lot of money and time down the road.

Mao: I agree. Once you have enough material to work with, you can start preformulation and formulation development for toxicology studies.

How much API is required for your screening program? What if I don't have enough API?

Mao: We usually require 2–5 grams of API for our IND Enabling Preformulation Package (IEPP), including compound characterization, physical form study, and preclinical formulation development. Because oftentimes the compound itself is very limited at the early stage, we can also do fit-for-purpose studies that require only 0.5 gram of API. We will quickly look at the compound's properties to see what the limiting issues are, develop solutions, and develop tox formulations for a specific type of study. It's also helpful for feasibility testing.

Do I need screening for drug delivery technologies?

Mao: As there is no one-size-fits-all solution, a screening for all enabling technologies is recommended. However, if the client already knows, for example, that the solid dispersion works the best, we can also go directly to solid dispersion formulation development.

What is the communication like among WuXi's various CMC departments and clients?

Mao: First, we have a dedicated project manager that connects the different functions in the CMC group that include drug substance, drug product, analytical as well as CMC writing teams. We have regular meetings both internally and with our clients to keep everyone on the same page.

Unlike many other global companies, WuXi has very centralized locations; we have four manufacturing R&Ds centers in the Shanghai area. Because the sites are in close proximity, we have very efficient material flow and information sharing, oftentimes through face-to-face meetings, which makes timelines very flexible and process streamlined.

Phimister: Many companies that advertise a kind of one-stop-shop that has been made through acquisitions, so functional units can be spread across the country or even in different countries. It almost feels like you're working with several companies.

How do we address the risks of the impact of pH and food effect when evaluating bioavailability? Are there other risks to take into consideration as well?

Phimister: This is a big area of research for oral drug delivery. It's important to know about these risks early on and to look at pH solubility profiles, including in fasted and fed-simulated intestinal fluids and gastric fluid. Measuring thermodynamic solubility gives you the worst-case scenario. It's also good to run a supersaturation assay to see how quickly it precipitates. That may give you the best-case scenario. From there, you can tell if you have a low-risk or a high-risk compound.

For food effect, is there more than a threefold difference from fed to fasted? And, is your bioavailability below 50% *in vivo*? If so, and you see a food effects, you should follow it up with specific food effect studies with animal models such as dogs or monkeys.

If the molecule shows high risks of food effect or high pH sensitivity, address them as early as possible and consider some more customized technologies even if they are more expensive to develop and manufacture.

Mao: Other risks you need to take into considerations are about dosage forms at later phases. When developing oral doses, consider patient factors early on, such as pill burdens, including pill sizes and dosing frequencies. For example, if the bioavailability isn't high enough, you might have to increase the drug load with a bigger pill size, which makes it more difficult to swallow and can affect patient's acceptance and compliance as well.

There are lots of ways to improve the bioavailability of poorly water-soluble drugs. How do you determine which one is best?

Mao: Firstly, we need to develop a full understanding of the physicochemical properties of the API, so that we can utilize the developability classification system (DCS) to understand what the limiting factor for low bioavailability is. For example, DCS Class IIA is dissolution rate limited so API particle size reduction may address the challenge well; when DCS Class IIB is intrinsic solubility limited, we will try solid dispersion and lipid formulation.

Again, every molecule is different. We suggest using drug delivery technology screening to decide the most suitable technology for your molecules. At WuXi STA, we have a full set of enabling technologies equipped with complete preformulation testing capability. So, we are confident we can select the optimal formulation for your molecule for best chance at success.

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