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WHITEPAPER

Setting a strong foundation for your oral solid dose product to support late-stage development

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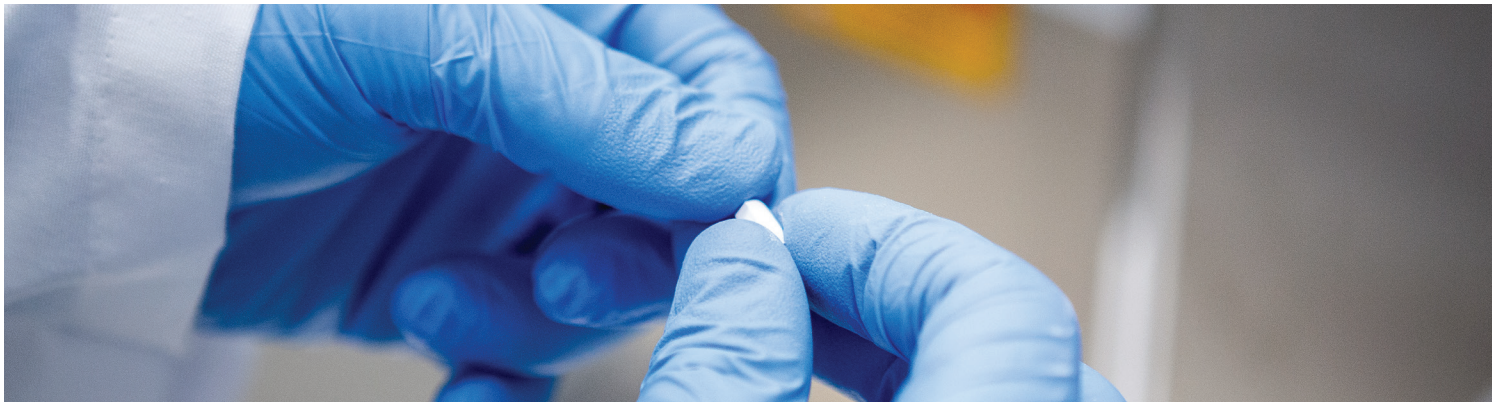
Abstract

Drug sponsors face significant pressure to reduce the time required to move a new molecule through Phase I and into Phase II trials. If all goes well, identifying the quickest scale-up path for supplying efficacy trials and commercial demands is next. But at early stage, sponsors need to keep the formulation as simple as possible. This means identifying the desired critical quality attributes of a formulation and selecting only those must-have requirements that align closest to the objectives of each clinical trial stage.



A race against time

For emerging pharma companies, and for those developing orphan products, the dividing line between first-in-human (FIH) safety studies and proof-of-concept (POC) clinical trials can be blurred. In a healthy volunteer study, a simple Phase I formulation may be used then improved for later patient trials. For trials in patients, a more robust formulation for shipment to multiple sites and countries is needed. For both cases, the opportunity for bridging studies on an improved dosage form may be limited. Regardless of study needs, however, there are formulation strategies to collect data that will reduce future development time.

Sponsors often ask a CDMO to supply a simplistic formulation available by a deadline, but this may not reveal the complexity of clinical study design, potentially missing the sponsors' real needs. Instead, a customized development strategy can be created when sponsor and CDMO collaborate on the details, planning for success (and surprises) and increasing the odds for a suitable and scalable formulation for Phase II and later clinical trials.

Early development strategies for oral formulations

Injectable formulations have the API already dissolved for introduction directly into systemic circulation. But for oral dosage forms, the API's physicochemical properties require several techniques to make a suitable formulation so that the API can be liberated for absorption and distribution. A poorly soluble API requires additional formulation development time. And when scaling up an early dosage form for automation, that pathway can only be estimated because the API properties affect the processing and formulation activities. These frequently change as API is scaled up, which will also affect the formulation.

The questions that sponsors need to ask themselves are: What is a "must-have" in the Phase 1 clinical trial? and What would just be "nice to have"? Fortunately, using phase-appropriate formulations and simple, flexible formats can minimize the time to start FIH studies. Data from strong preformulation studies in these early stages can accelerate selection of the Phase II clinical formulation.

Clinical trial objectives

In Phase I, the primary objective is to demonstrate the safety and tolerability of the API when it is administered in single- and multiple-ascending doses (SAD and MAD, respectively) in healthy volunteers or patients. Secondary goals can include characterizing the PK profile of the API, the dose-response relationship, and maybe a food effect. The number of subjects in a Phase I trial varies up to approximately 100 subjects.

In Phase II, dose-ranging (typically in 100-300 patients) is conducted to assess the API's effects against a validated clinical endpoint. Sponsors may manufacture one large clinical batch or several smaller batches to support enrollment. So much will change before getting to Phase III, where sponsors seek to demonstrate efficacy in 500-1000+ patients in a well-controlled study. In addition to the dosage form, numbers of doses, and the release profile, the manufacturing scale will also change. Rarely is a Phase I formulation used in Phase III, so formulation strategies should build in complexity only when needed to support that next stage.

Impact of clinical study designs on CMC

As mentioned above, collaborating with your CDMO on all clinical details (e.g., enrollment and dosing schedules) can give the sponsor customizable and phase-appropriate options to supply the clinical sites. Increasingly these days, though, Phase I trials are more complex than most CDMOs realize, and thus, the formulation strategy must align with the clinical design.

A multi-site clinical study needs both drug product and an appropriate packaging, labeling, and shipping strategy.

Both sponsors and CDMOs should carefully review important questions about the clinical study, such as:

- How many dose strengths are needed for the trial?
- What is the duration for each SAD and MAD cohort and the total trial?
- Will there be only healthy volunteers or patients, or will volunteers, then patients, be part of the study?
- How many different sites and countries are included in this Phase 1 trial?
- Will all sites start dosing at the same time?
- Are there multiple indications and/or protocols for this trial?

A SAD/MAD study conducted at one clinical site would only need one delivery of several active strengths and a visual placebo with stability for a year or less. If the trial includes global enrollment then the CMC plan needs to cover the regional regulatory standards of each country and longer stability.

A multi-site clinical study needs both drug product and an appropriate packaging, labeling, and shipping strategy. Sharing the clinical distribution plan with your CDMO can prevent drug product shortages that delay completion of Phase I and start of Phase II. In fact, this critical information ensures that sponsors order enough API to support formulation development throughout clinical manufacturing and packaging.

Oral drug formulations frequently change during clinical development

One of the misconceptions that many clients have is that the preclinical and clinical formulations must be identical. While convenient, this is not a requirement, and sponsors should embrace phase-appropriate formulation strategies for all stages. For example, a client might use a lipidic solution in the preclinical studies to maximize PK exposure, but an API-in-bottle in the FIH trial is perfectly acceptable.

Another common misconception is that switching formulations between clinical phases requires a separate “bio-equivalency” study in both the preclinic and clinic. One option is to compare the new formulation against the old one using a bridging clinical study, either as a stand-alone exploratory PK study or as part of an ongoing patient study.

Phase I yields the first data set on how a new API behaves in the human body, giving us the best guidance on the attributes of the Phase II formulation. A strong preformulation package in Phase I can de-risk and shorten the development time required for the Phase II formulation. As previously mentioned, the physicochemical properties of the API strongly influence the formulation. The API may be crystals with very good flow properties, or there may be needles with poor flow properties. Thus, the following properties are essential when developing drug products:

- Morphology
- Particle size
- Powder flow and bulk tap density
- Physical and chemical stability
- Solubility
- Degradation impurities
- Reactions with excipients
- Process variables

Drug products used for FIH studies can simply be an API-in-bottle or API-in-capsule, or similar for a blend. Sometimes an immediate-release tablet is better because it is more robust. Soft gelatin capsules are sometimes considered for Phase I trials, but the lipidic formulation itself could simply be dosed as an oral solution for quicker trial start.

Potential approaches for preclinical and FIH formulations

Preformulation studies on the API help define potential formulations, and simple formats that are chosen for FIH can be scaled up for Phase II. As shown in Table 1, the added complexity increases the number of required analytical methods and the development time.

By working with the simplest of the formats, an oral formulation suitable for Phase I can be developed and manufactured in as few as 14 weeks using Thermo Fisher Scientific's Quick to Clinic™ program. These formats — API or a blend-in-bottle or in-capsule — lend themselves to speed to clinic. Figure 1 below shows that, shortly after the API and the analytical methods are received, prototypes and one month's stability using fit-for-purpose analytical methods are generated.

More importantly, the clinical packaging and labeling were designed in parallel with development, so that a finished packaged dose is ready to be released and sent off to the clinical site.

Increasing complexity ↓

Formulation approach	Purpose	Challenges
API or blend in bottle	Simplest format, quick entry to clinic	Poor wetting; risk of food effect; limited scalability; mixing instructions and in-use stability
IR blend (wetting agents, flow aids) in bottle	Improve dissolution Increase solubility Reduce PK variability	Weak base: precipitation at high pH
Solubilized: lipid solution in bottle	Increase C_{max}/AUC Inhibit precipitation Reduce food effect	Supersaturation (but dose can be reduced) Drug loading limit
Solubilized: SDD powder in bottle for reconstitution	Increase C_{max}/AUC Inhibit precipitation Reduce food effect	Supersaturation (but dose can be reduced) Drug loading limit

Table 1: As the formulation approach increases in complexity, so too do the number of required analytical methods — and time to program.

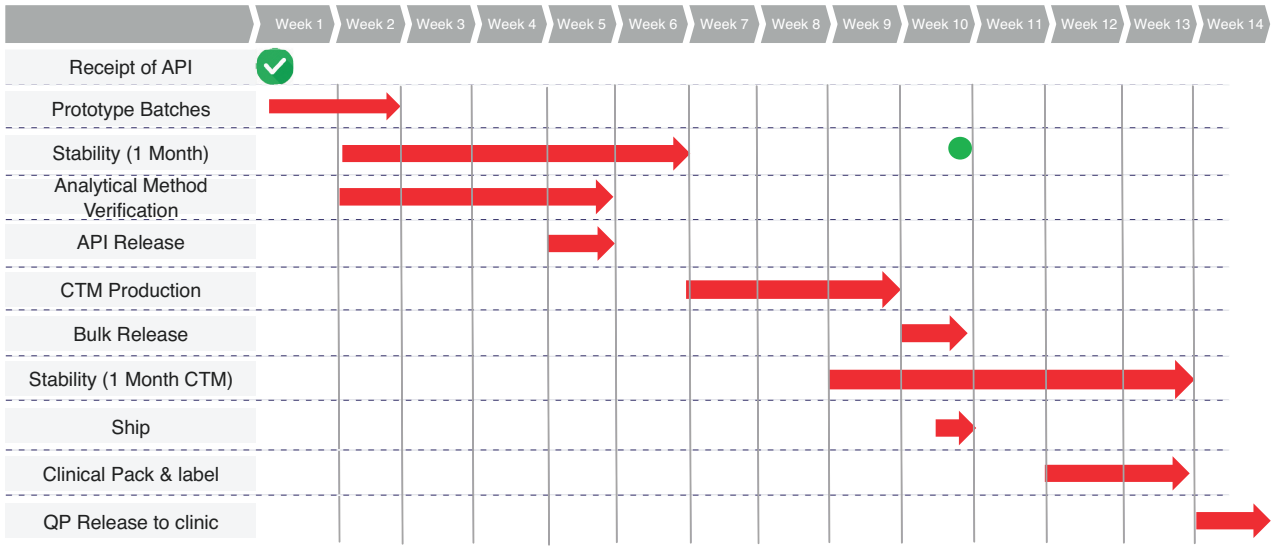


Figure 1: Thermo Fisher Scientific Quick to Clinic™ timeline for oral solid dose

How much API is required for an FIH study?

Sponsors should talk about drug product before they order their API, because frequently they do not have enough available to support formulation development and clinical supply. For a typical two-species preclinical study to support IND/CTAA with a healthy volunteer FIH program with maximum human dose not exceeding 500 mg, a single GMP batch of 7 kg should be sufficient. Sometimes, high-quality engineering API can be used to support the formulation development, making more GMP API available for the clinic.

Options for poorly soluble drugs

The success rate of a new molecule moving through Phase I on to approval significantly decreases when going from Phase I (30%) to Phase II (14%), with only 1 in 10 molecules making it to Phase III. Molecules coming out of discovery with poor aqueous solubility and/or bioavailability face the greatest risk of failure. Of the many options available for formulating poorly soluble drugs, which option should you choose, and why?

Table 2 outlines the various enabled formulation technologies available, but a one-at-a-time approach could take months of effort on an unsuitable technology.

Computational methods can accelerate formulation development, focusing only on those potential pathways that are more likely to be successful. In a recent case study, a client had a library of seven new chemical entity (NCE) leads with high target activity. Worried about expected low aqueous solubility in these molecules, the client needed to select one NCE for the toxicology batch. We applied our computational service (Quadrant 2™) to study three of the seven NCEs from a range of chemical space. With just the molecular structures, we predicted the aqueous solubility and selected the best formulation technologies and excipients, delivering a report and plan in only two weeks. This approach shaves off weeks of laboratory experiments that waste precious API in trial-and-error efforts. The molecular classes were all determined to be DCS class IIb; lipids were recommended for two of the NCEs, and amorphous SDD for the third. The client selected the lead compound for the toxicology batch and had a formulation plan for their IND-enabling preclinical studies.

We applied our computational service (Quadrant 2™) to study three of the seven NCEs from a range of chemical space.

Technology	Attributes	High-level considerations
Salts	Simple transformation, can increase solubility and stability	PK comparison of salt and free acid/base; full physchem and SS characterization on each
Spray dried dispersion (SDD)	Broadly applicable, standard solid oral dose manufacture	Excipient and solvent selections, process conditions
Hot-melt extruded dispersion (HME)	Solvent-free, continuous process	Range limited of compounds/excipients; multidimensional process space, API thermal stability key
Coated beads, dispersion	Standard coating equipment (fluidised bed)	Best for low-dose formulations; excipient and solvent selection
Lipids	Broadly applicable	Complex formulation space, empirical development process
Size reduction (Micronisation, nanoparticles)	Crystal form retained, controlled crystallisation or simple mechanical process	Limited range of compounds, formulation complexity for nanosuspensions, dosage form design
Amorphous	No excipients required	Limited range, physical and chemical stability
Co-crystals	Crystalline API, stability and solubility advantages; standard solid oral dosage forms	Screening approaches customised, control challenging
Complexes (cyclodextrins, mesoporous substrates)	Can be simple	Limited range, drug loading and dosage form design considerations, process approach

Table 2: Technologies available for poorly soluble drugs

Enabled formulations in FIH studies can be dosed in a simple format; a unit dose (a tablet or capsule), is not required for a Phase I study unless other factors dictate the need for it. For example, a lipidic formulation can be accurately dosed by oral dropper or cup in a healthy volunteer clinic or manufactured as liquid-filled hard gelatin capsules if needed. Likewise, SDDs are suitable as powder-in-bottle or converted into a capsule or tablet. For comparison purposes, a reconstituted SDD powder should always be tested in a clinic against the formulated capsule or tablet; this could help understand if the SDD or the unit dose gives poor PK exposure. In general, the development of an enabled formulation can add approximately three to four months to the timeline.

Post-FIH trial success: What next?

To a CMC lead, clinical studies may seem like gating exercises that answer “Go” or “No-go” on the next CMC milestone. But Phase I pharmacokinetic results indicate what is needed in the next clinical formulation, such as improved solubility or a different release rate. And as mentioned before, formulation and process will almost always be changed to support scale-up on automated manufacturing equipment for Phase II.

Another consequence of clinical scale-up is potential changes in the properties of the API that can affect the drug formulation and process. A thorough preformulation study of the first batches of API gives comparison data against the new lots, enabling quick and informed decisions for moving from small to large scale.

In summary, FIH studies are more successful when both CDMO and sponsor agree on what are must-haves in the drug product development plan and then decide what would be a value-add in the formulation and study. These actions ensure quicker time into clinic by the use of simple, phase-appropriate formulations. Assessing the risk to achieving primary clinical objectives also helps the sponsor and CDMO outline a development strategy together that includes mitigation approaches to overcome any challenging API properties. Finally, by making use of phase-appropriate formulations and leveraging predictive tools to select best-in-class technologies that shorten development times, sponsors will position themselves for success in their Phase I studies and beyond.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 55 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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Kevin provides technical consulting for drug delivery, early formulation development programs, and scale-up. He focuses on finding solutions that align with a client's clinical study design for small molecules with biopharmaceutic and physicochemical challenges. Kevin brings more than 25 years of industrial experience in synthesis, formulation and solubilization technologies (oral and sterile), and adaptive clinical studies, having worked as an independent consultant and as a scientist at various CDMOs in addition to his 9 years at Thermo Fisher Scientific's Pharma Services business. Kevin has a PhD Inorganic Chemistry (Ohio University), MS Polymer Chemistry and BS Chemistry (Texas State University).

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