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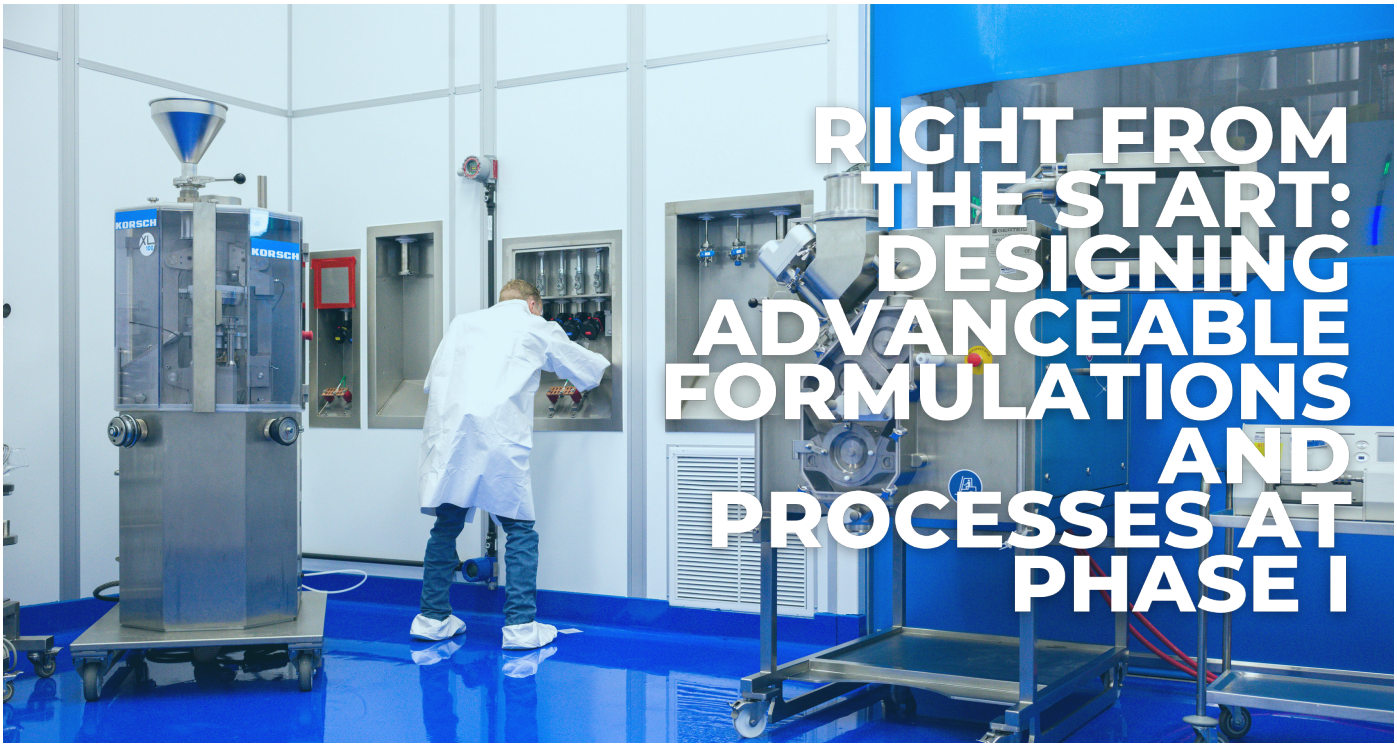


RIGHT FROM THE START: DESIGNING ADVANCEABLE FORMULATIONS AND PROCESSES AT PHASE I

ARTICLE

Abstract

The primary criteria for successful drug development and commercialization have long been established: any new pharmaceutical product must be safe and effective, and it must be both manufacturable and commercially viable. Historically, demonstrating safety and efficacy was sufficient to advance a drug candidate through clinical trials. However, as timelines have accelerated and the market continues to become more competitive, the risks associated with manufacturability and commercial viability have drawn more attention, and drug developers are increasingly seeking approaches to address these concerns at earlier stages of product development. This shift in emphasis and timing demands an appropriate deployment of tools, processes, and methods, which means establishing partnerships with contract development and manufacturing organization (CDMO) partners who share this vision. In this new landscape, success hinges on the ability to navigate the intersection of science, technology, and commercial readiness, driving an increasingly proactive and agile approach to drug development.

Many Benefits to Advanceability Early in Development

Accelerating the development of a candidate drug from discovery to commercialization by even a single year can bring breakthrough therapies to individuals with limited treatment options, especially if this candidate addresses an unmet medical need. Moreover, the ability to rapidly navigate the regulatory landscape and reach the market can enable healthcare providers to respond more effectively to emerging health crises, obtain easier access to innovative treatments, and be better equipped to tackle the evolving needs of patient populations.

Reducing development time by a year or more can also translate into the preservation of hundreds of millions of dollars in potential revenue, considering the finite duration of patent protection. In this realm, the significance of speed cannot be overstated, as swiftly entering phase I and II studies not only reduces developmental timelines but also unlocks the prospect of significantly higher revenue generation.

Traditional drug development strategies prioritize initiating clinical trials as rapidly as possible to promptly identify any safety-related shortcomings, which is often referred to as the "fail fast" approach. With the arsenal of advanced preclinical models available today to investigate drug safety, including animal studies, cell-based assays, and non-empirical in silico simulations, such concerns can largely be allayed even before a drug reaches clinical trials. This has enabled a shift in focus to efficacy rather than safety in early clinical phases. In fact, it is commonly understood that the vast majority of phase I drugs progress seamlessly to phase II, where efficacy evaluations traditionally take center stage.

In this shifting landscape, pharmaceutical companies increasingly opt to assess drug efficacy or biomarkers as early as phase I rather than waiting for phase II studies for such insights. However, the decision to halt clinical testing owing to an early lack of efficacy remains challenging. This hesitancy is due to the potential for drugs to show greater effectiveness in larger and more diverse patient groups in phase II trials, where variations in patient responses can provide a clearer indication of a drug's potential.

However, the choice to advance into phase II without conclusive early efficacy data poses significant challenges in decision making around chemistry, manufacturing, and controls (CMC). These CMC complications are particularly pronounced for oral drug formulations, which may not easily scale up for larger studies, may not consistently exhibit the desired therapeutic effects across different patient populations, and often require complex analytical methods to ensure quality and consistency.

"The traditional 'fail fast' approach in drug development is evolving,"

explains Dan Smithey, Ph.D., founder, President, and Chief Executive Officer of Serán Bioscience.

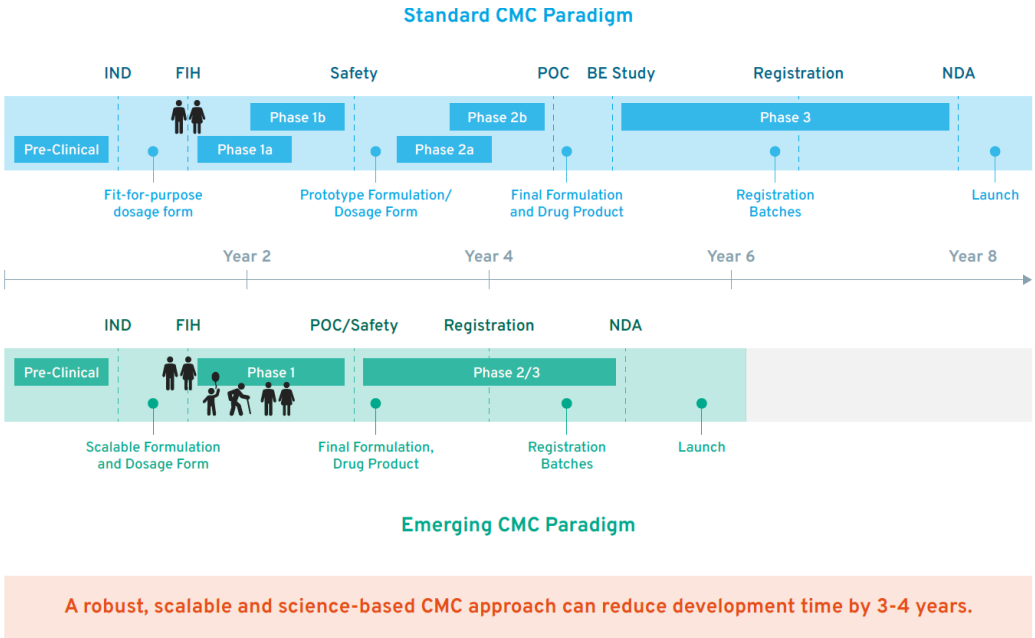
The solution to this problem lies in designing phase I programs with a robust CMC approach to ensure that they can transition seamlessly into phase II and ultimately into phase III and commercialization. Failing to consider advanceable formulations and processes during the early development phases not only jeopardizes a product's potential value but also diminishes its marketability. Furthermore, the subsequent scale-up of suboptimal processes and formulations for late-stage and commercial production increases the risk that reformulation will be necessary.

"The traditional 'fail fast' approach in drug development is evolving," explains Dan Smithey, Ph.D., founder, President, and Chief Executive Officer of contract development and manufacturing organization (CDMO) Serán Bioscience. "It has become essential to emphasize early-phase commercial readiness to ensure that formulations and processes are not just scientifically sound but also commercially viable right from the start. This strategy mitigates risks and paves a smoother path toward successful market entry."

Flexibility and Speed are Essential

Flexibility and speed are paramount in drug development. It is essential to make sure that both the formulation and the process are sufficiently flexible to adapt as the program evolves through clinical development to commercial manufacturing. A formulation that is flexible enough to facilitate easy scalability and dose strength adjustments, in addition to accommodating diverse patient populations, can support rapid advancement through clinical trials and ultimately commercialization without the need for reformulation. Establishing flexible formulations and processes can circumvent the need for relative bioavailability (RBA) studies by eliminating the necessity to overhaul the formulation and process as the candidate progresses into later clinical trials. This can significantly reduce development timelines, often by as much as three to four years, and shift the focus from reformulation to process development and scalability. "Integrating material science principles into drug development is not just about technical excellence; it's about foreseeing and preparing for the commercial and clinical journey of a drug," Smithey adds. "The goal here is to never let CMC be a bottleneck. The clinical patient data should be the limiting factor in the speed to market, not your CMC team."

The most compelling solution to maximize flexibility leverages tablets as the primary dosage form, owing to their superior



Serán's Emerging CMC Paradigm Shift©

large-scale manufacturability, robustness, coating ability, and higher dosage strengths, which can lower pill burden compared to capsules.
ward manner.

A key focus at Serán is ensuring that we can rapidly develop tablet formulations in which we have a high degree of confidence from the beginning -- with very limited material,"

explains Erica Schlesinger, Ph.D., Serán's Vice President of Technical Development.

I"People tend to worry that tablets are too difficult to make and have a high barrier to entry," explains Erica Schlesinger, Ph.D., Serán's Vice President of Technical Development. "At Serán, we are experts at developing tablets quickly with methods that allow us a lot of flexibility. That barrier doesn't exist in our world. Our goal is to find a way to make tablets more accessible."

Contrary to what many believe, tablets can be developed rapidly and with limited material through the evaluation of material properties in formulation screening and the identification of scale factors. Factors such as compressibility, tabletability, and compactability (CTC) can be influenced by the selection of excipients, tablet architecture, and processing techniques. Modern tools like the STYL'One Nano (Korsch) permit the assessment of material properties with just one or two tablets, furnishing valuable information to guide the scaling process in a relatively straightforward manner.

Well-designed tablet formulations can also offer the flexibility to adjust dose strength over the broad range that may be required to support clinical development. A common formulation may be used to support dose strengths over a 10-fold range, just by adjusting tablet weight and geometry.

A strategy combining two common formulations evaluated in early clinical studies provides even greater flexibility in dose range, as well as coverage of a formulation range that allows for refinement of an optimal tablet design once late-phase and commercial dose strengths are selected. This often eliminates the need for RBA studies and allows for analytical methods and stability data from early-phase studies to inform and support the late-phase and commercial product. "A key focus at Serán is ensuring that we can rapidly develop tablet formulations in which we have a high degree of confidence from the very beginning — with very little material," adds Schlesinger. "There's a misconception that tablet development is inherently slow and complex. At Serán, we break this stereotype by rapidly developing tablet formulations that offer extensive scalability and dosing flexibility. Our expertise in material science allows us to navigate this process swiftly, making tablets a more accessible and attractive option for our clients."

Early-Phase Commercial Readiness at Serán Bioscience

At Serán, discussions with clients about clinical development strategy and commercial product design typically begin before phase I. Serán's team works with the sponsor to define a target product profile (TPP) through a meticulous evaluation of the indication, the intended patient population, and other integral aspects of the client's strategic vision. As the API is characterized to determine the most suitable formulation technology and drug product design, the team must thoughtfully consider the final TPP, as it is the foundation for the entire development path and strategy, while identifying which aspects of the TPP must remain flexible during early clinical development.

Development of advanceable formulations and processes in phase I must be achievable with rapid timelines and limited material. Serán excels in efficiently applying material-sparing approaches and customized development plans, tailoring the company's strategies to each project's unique needs and constraints.

As clinical development progresses, process optimization, and scale-up is expected, but with the formulation design space and unit operations for manufacturing defined early, these activities can build toward a well-defined operating space with demonstrated performance in a cGMP environment while ensuring scalability and flexibility.

All these pre-registration activities are being executed using the product life cycle approach as part of Stage 1 Process Validation (PV) as stipulated by global regulatory agencies.

This maximizes the utilization of stability and analytical method data across all phases of clinical development to the commercialization stage, leading to real savings in terms of time, resources, and finances. Additionally, this approach provides for identification and control of critical quality attributes, which in turn provides for seamless execution of PPQ activities to support commercial launch.

It is worth emphasizing that, even for clients with late-stage candidates, where projects prioritize late-stage development and commercial viability, the methodology applied at Serán is consistent with that employed for phase I candidates. Many of these late-stage projects are brought by clients whose candidates have already progressed into clinical trials (typically phase I/II) but were not designed with the flexibility necessary for commercial advancement. Consequently, there is a demand for commercially viable formulations, which could involve reducing pill burden, enhancing performance, increasing drug loading, bolstering manufacturing robustness and stability, or transitioning to more patient-centric dosage form. For these late-stage projects, Serán applies the same approach used for phase I endeavors, leveraging analogous bench-scale techniques and study designs, armed with a wealth of preliminary information to inform the development process and enable rapid advancement into RBA studies with an advanceable formulation and process.

Bringing Value to Customer Products Today

Smithey sums up the changing drug

development mindset and Serán's approach to maximizing speed and flexibility as follows:

"There has been a paradigm shift in how drug development is done, moving away from a "fail fast" approach; this shift necessitates a shift in how drug products are developed. Serán brings that drug product development earlier to support early studies by removing the barriers — cost, speed, and flexibility — that are conventionally thought to hinder the development of oral solid dosage forms. By leveraging material science principles and our expertise to develop formulations and processes that are scalable and advanceable from the outset, we can provide our clients with flexible formulations and processes that can support their program as clinical study needs evolve and ensure that all R&D resources are effectively channeled toward assets with the highest probability of yielding optimal returns."

Serán is a world leader in drug development and manufacturing. Utilizing a foundation of physical and chemical science, Serán designs robust formulations and engineering solutions to some of the industry's toughest drug product problems.

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