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WHITEPAPER

Expediting early-phase development of small molecules: An integrated approach

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Executive summary

Small molecule drug development has changed substantially in recent years. With the heightened focus on molecularly targeted therapies, small molecule active pharmaceutical ingredients (APIs) and drug products are more complex and potent than ever, requiring increasingly specialized manufacturing processes and drug delivery solutions. At the same time, the competitive demand for rapid entry into clinical development—combined with accelerated review pathways—translate into compressed manufacturing and delivery timelines.

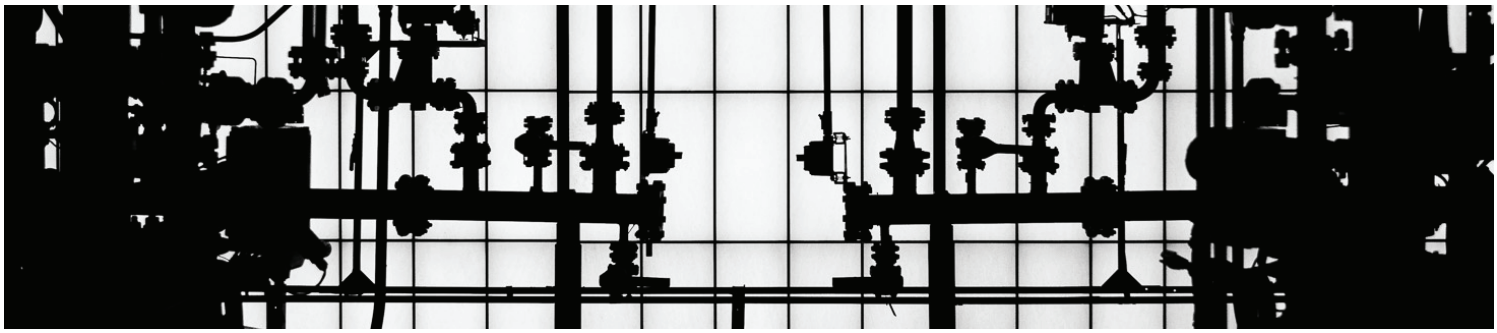
These dynamics challenge sponsors to balance the need for speed with optimal execution of chemistry, manufacturing, and control (CMC) activities to ensure the quality of the finished product during all phases of development. Achieving this balance is particularly challenging for new and emerging biopharma companies who are dominating the pipeline and opting to hold onto their molecules possibly through commercialization. Without the resources, expertise, and bandwidth of large pharma, these companies rely on strategic partnerships with consultants and contract development and manufacturing organizations (CDMOs) to support their development programs.

The more distributed the development team, however, the more risk there is in advancing molecules to initial clinical studies. In many cases, drug substance, drug product, and clinical strategy activities are spread across multiple companies or consultants. This translates into multiple technology and process transfers across the development lifecycle and introduces multiple points of potential vulnerability. Minimizing risk while accelerating progress to clinic requires a collaborative approach to project execution built on an understanding of the process and science involved in each phase of development and the impact that phase-specific decisions have down the line.

In this whitepaper, we discuss key strategies for efficiently advancing small molecules from API to pre-clinical data and clinical supply, including the following:

- Early planning to understand the scale-up and technology transfer needs at each phase of development
- A program roadmap built on a thorough understanding of the molecule's properties and the impact on formulation choices
- Flexibility in manufacturing operations to accommodate changes in materials, scale, and process variability associated with technology transfer
- Integrated CMC capabilities to support drug substance and drug product development and GMP manufacturing from first-in-human (FIH) to Phase III clinical development

These considerations minimize the timelines, complexity, and risk associated with the development and manufacture of small molecule drug substances and drug products, thereby enabling biopharma companies to deliver therapeutics to clinic more quickly and compete effectively in the modern pharmaceutical marketplace.



Introduction

Changes over time have brought the small molecule drug development market to its current focus on molecularly targeted therapies, making small molecule active pharmaceutical ingredients (APIs) and drug products more complex and potent than ever. And the market keeps growing.

The small molecule competitive landscape is currently estimated at around $32.15 billion and is expected to increase to more than $50 billion by 2026[i]. Historically, large pharma led most small molecule drug development, funding and executing nearly all activities from development to commercial. Today, new and emerging biopharma companies are playing a growing role in the overall market, holding onto molecules longer, often with the hopes of seeing them through Phase II clinical trials, if not all the way to commercialization.

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Current pipelines are boosted by a growing number of small molecule preclinical candidates, and there are more Phase I trials now than ever before. Relative to large molecules, small molecules are quite complicated to develop, with a major challenge being obtaining enough API to support trials while simultaneously determining the required dose strengths. This complication can be exacerbated by the intense need for speed in today's market, particularly in areas of unmet patient needs such as oncology and orphan diseases.

As noted, new and emerging pharma companies are driving a lot of the action in the market today. Because the laboratory capacity and pool of expertise can be a limiting factor in these companies, there is a corresponding increased reliance on CDMOs. Accelerated review pathways, shorter exclusivity periods, and milestone-based funding further drive the need for collaboration with a CDMO who can offer a wide range of expertise in chemistry, manufacturing, and controls (CMC) in order to mitigate development risks and maintain timelines and budgets.

Development process and handoffs

From development to API to drug product to clinical supply, seamless hand-offs are critical to the overall success of a program. Each of the key components required for first-in-human (FIH) studies for small molecules—drug substance development and supply, solid-state characterization/bioavailability enhancement, and phase-appropriate drug product in powder-in-capsule, powder-in-bottle, liquid-filled hard capsule or tablet format—requires understanding of a unique set of considerations.

Sometimes each handoff is associated with a different, specialized CDMO and any lack of coordination or communication can be detrimental to budgets, timelines, or even quality of the product. A single CDMO with integrated support capabilities specifically reduces tech transfer vulnerabilities, which are particularly troublesome with respect to the increased complexity of today's small molecules.

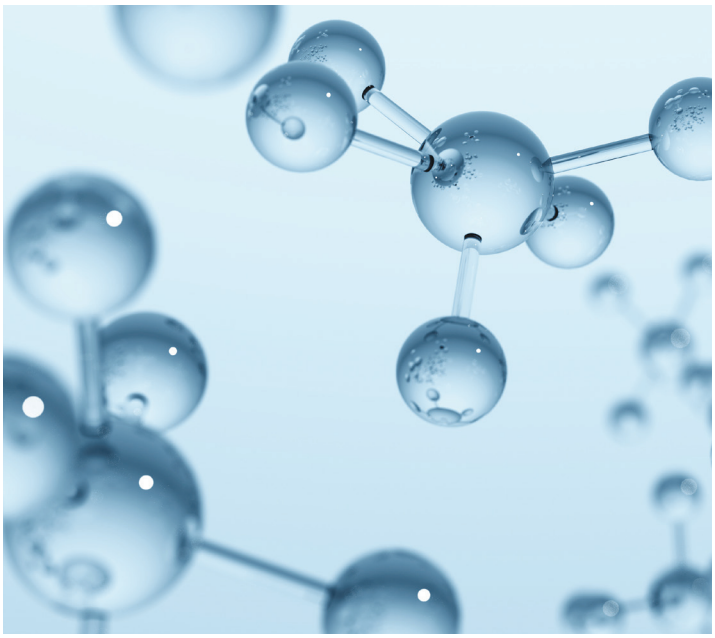
Strategies for navigating early manufacturing processes

Every API is different, and each development process will have its own unique challenges and opportunities. Yet, there are a few key strategies that apply broadly and can help developers navigate the early manufacturing and production process while mitigating risk and ensuring quality. These include early planning, a science-guided roadmap, manufacturing flexibility, and an integrated drug substance to drug product process.

Strategy 1

Early planning

The first phase of a preclinical development program for small molecule drugs is the manufacture of the API but planning for a successful program should start with the end in mind: the clinical objectives. These clinical objectives should drive the drug product strategy, and drug product strategy should drive API strategy. Thoughtful early planning that incorporates the unique needs, risks, and opportunities associated with each stage of development can then translate into well-informed timelines and task lists. Starting with the end in mind ensures that each step along the way aligns with the correct path to the desired outcome, rather than increasing time and cost with unnecessary errors or diversions.



Indeed, early investment in development can yield downstream dividends in API development. Of course, the specific molecule will dictate the details of the process that must be followed but addressing the considerations below can provide value to potential partners and regulatory authorities:

- Smart selection of regulatory starting materials
- Use of a synthetic process that avoids overly hazardous reagents or problematic impurities
- Avoidance of intermediaries with genotoxicity potential
- Consideration of scalable chemistry and the potential for convergent synthesis
- Solid-state characterization and early selection for a form based on a thorough solid-state screening study
- Early decision on final isolation solvents
- Early initiation of analytical method development activities

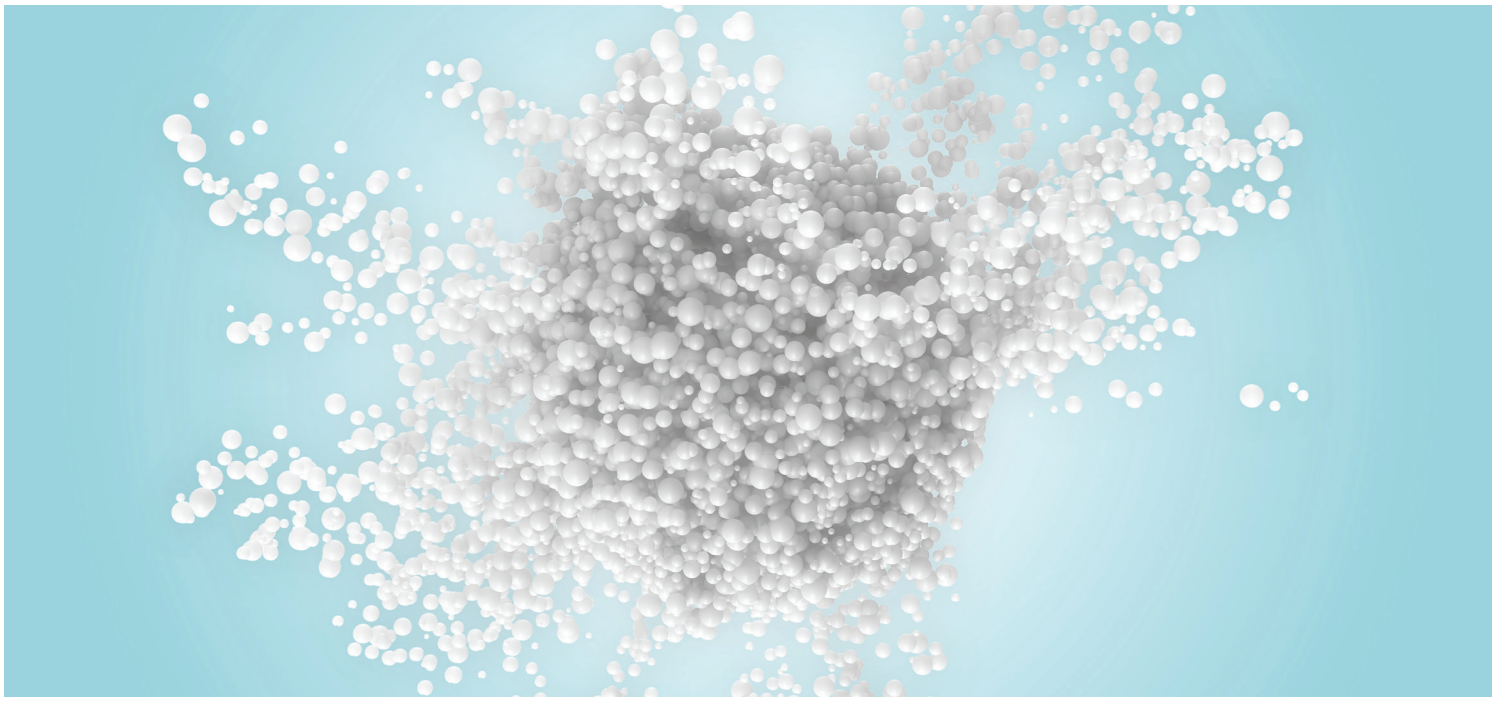
Communicating these considerations clearly with all stakeholders is part of early planning and effective collaboration. Enable your stakeholders to be true collaborators by sharing all of the data. Without this open communication and complete sharing of knowledge and planning, important details can be lost.

Strategy 2

A science-informed roadmap

A program roadmap built on a thorough understanding of the molecule's properties and the impact on formulation choices is critical to success. Each stage of clinical development has unique demands on the API that must be considered:

Pre-clinical, pharmacokinetics (PK) and toxicology. It is important to note that preclinical and clinical formulations are not required to be identical. An enabled formulation, for example, where the API is fully dissolved in a clinically acceptable solvent for preclinical studies can be used to assess toxicity and PK, even if the clinical trial will use an aqueous suspension of the API.



Single-ascending dose (SAD) studies

Again, clinical formulations are not required to be identical between phases. To assess safety and tolerability, Sponsors may opt for a finished dosage form, but simple formats (e.g., API in a bottle for suspension or a simple capsule) are frequently used to start trials rapidly to assess safety and tolerability. Within the SAD stage under a flexible protocol, though, a different formulation can be evaluated for comparable PK exposure at a previous safe dose level in a new cohort. If acceptable, this new formulation can be used in subsequent SAD and MAD periods.

Multiple-ascending dose (MAD) studies

Here, the safety and effects of steady-state dosing are evaluated, using the simplest form of the API or a formulated drug product.

Proof-of-Concept (POC)

Use a stable unit dose for POC conducted at remote specialist sites. Opportunities exist for flexibility in formulation and clinical study. Depending on the approved clinical strategy, Sponsors may pivot quickly to POC studies whilst completing the SAD/MAD stages.

Understanding the needs for each of these stages helps determine the amount of API needed for preclinical and Phase I studies. Data gleaned from these stages should be shared with all stakeholders to ensure alignment and take advantage of their extensive development expertise.

Strategy 3

Manufacturing flexibility

Flexibility in manufacturing operations allows developers to accommodate changes in materials, scale, and process variability associated with technology transfer. Collaborating with strategic partners who can anticipate the amounts of API and DP required for complex formulations and the potential needs for change along the way creates the agility needed in manufacturing operations and supports smoother scale-up.

Strategy 4

Drug substance to drug product integration

Decades of experience in drug development have inspired new solutions for supporting drug development from early stages to clinical supply. Collaboration between drug substance and drug product teams helps ensure that the optimal end formulation is kept in mind throughout the entire development process and that every step in the API stage is a benefit to the DP stage. This includes timeline management and data sharing.

When determining the best way to integrate drug substance and drug product development, the following behaviors are key:

- Ensure the lead compound(s) can be manufactured in sufficient quantities to support initial toxicology and preclinical studies.
- Be equipped to scale up the manufacturing processes to produce clinical drug substance to good manufacturing practice (GMP) standards.
- Understand the chemistry of the impurities which can have impact on the toxicology profile and the purity of the compound.
- Ensure availability of raw materials.
- Assess manufacturing capacity.
- Prepare for bridging substance to product.
- Establish workflows and processes.
- Identify and involve stakeholders (formulation scientists, solid state chemists).
- Prepare a data sharing strategy to ensure rapid drug substance, dosage form design, and drug product manufacturing.

Single vendors with high-quality project management can shorten development cycles and reduce costs, saving an estimated 19 weeks for small API through Phase 1 compared with a multi-vendor model.

The benefits to this integrated approach are many. They include timeline acceleration through integrated timelines, cross-site collaboration, and elimination of duplication of work and gaps between activities. Integrated services can offer tech transfer reliability, supply chain control, streamlined supply chain, streamlined regulatory activities, and reduced risk. Other benefits are derived from the expertise and experience leveraged across a broad network of stakeholders and centralized logistics and storage with enhanced liability coverage.

Coordinating API, DP, and clinical packaging services with one vendor under a single contract further de-risks clinical development for both large and small clients. [ii]Single vendors with high-quality project management can shorten development cycles and reduce costs, saving an estimated 19 weeks for small API through Phase 1 compared with a multi-vendor model model. Further benefits can be gained from aligned clinical distribution services.

Conclusion

Over the past two decades, CDMOs have become an integral part of almost every drug development program. For biopharma, CDMOs are strategic partners, providing expertise, consultancy and capabilities that are fully integrated with their own pre-existing activities. Yet, there is the potential for the formation of functional silos, particularly when multiple partners are engaged. These silos (e.g., drug substance versus drug product) can slow down the development process. Seamless coordination through integrated services for drug substance and drug product manufacturing offers a more agile approach resulting in a more efficient and accelerated development plan.

Further, aligning the clinical packaging, DP, and API teams enables:

- Sufficient supplies for the clinical program
- The ability to flex schedules up and down the team by efficient communication
- Seamless handoffs between collaborating teams
- Significant time and money saved

As we continue to understand the growing needs among patients, and as molecules become more complex and timelines shorten, the importance of finding new solutions to tighten development processes becomes clearer. The adoption of an integrated drug substance, solid-state characterization, and phase-appropriate drug product development strategy can support a simplified and accelerated route to FIH studies.

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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 65 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. Built on a reputation for scientific and technical excellence, we provide pharma and biotech companies of all sizes instant access to a global network of facilities and experts across the Americas, Europe, Asia, and Australia. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic™ programs for large and small molecules help you balance speed and risk during early development so that you can file your IND quickly and successfully. Digital innovations such as our mysupply Platform and Pharma 4.0 enablement offer real-time data and a streamlined experience. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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