The Delicate Dance: When Phase-Appropriate Decisions Carry More Risk

In early drug development, some of the most critical decisions are akin to a choreographed dance between two partners — moving in sync allows each performer to maintain balance and deliver on audience expectations, even during the most complex and technical routines. In both scenarios, each move must work in the moment while also serving the larger vision for the "performance."



However, this can be difficult to achieve in a drug development program when many decisions are driven by the need to meet investor milestones that dictate whether you have financial support for the next stage. A phase-appropriate approach can help relieve some of that pressure by focusing efforts on the current stage rather than investing too much time and resources when the risk of failure is still high.

Yet, the impact of some process development and analytical decisions can be felt well beyond the phase in which they were made. While that doesn't mean you have to plan the full commercial process from the outset, it does mean knowing how to safely prioritize today's requirements without compromising tomorrow's outcomes.

Looking Beyond the Next Milestone

Heavily favored by most global regulators, phase-appropriate drug development recognizes what decades of scientific research has taught the modern pharmaceutical industry: We don't know what we don't know.

Product and process knowledge are not established criteria at the start of a development strategy but understandings that develop over time, as each stage brings new information to light that can inform decision-making. The question is where and when within that evolving context teams should account for both immediate process considerations and future priorities.

Three areas warrant particular attention because of their potential long-term impact:

Route of Synthesis

The route of synthesis is one of the earliest and most important decisions in drug development. A comprehensive stress test on a chemical synthesis process to find which path to market is most suitable can help bridge the gap between an idea at bench-scale and a commercial success at large-scale. Through route scouting, you can define a workable approach to producing the molecule as well as the basis for each process development decision that follows.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance development and manufacturing across the entire drug lifecycle, as well as comprehensive analytical services.

With over 45 years of experience and a team of 2,000 experts servicing global clients from North America and Europe, Cambrex offers a range of specialized drug substance technologies and capabilities, including continuous flow, controlled substances, peptide synthesis, solid-state science, biocatalysis, material characterization, complex synthetics, and highly potent APIs.

Raw Material Selection

Like any recipe, the quality of the final product depends on the starting materials: select the right ones, and they support the process as it scales; select the wrong ones, and challenges may only compound as scale increases. Some reagents that seem relatively inconsequential in the early stages can have a significant impact later, specifically on critical quality attributes like product potency, purity and glycosylation profiles.

Synthesis Operations

The operational aspects of the synthesis, reaction conditions and isolation techniques also deserve careful consideration, as the choices made here could set specific manufacturing requirements for the API.

Reaction conditions from cryogenic or high temperatures, for example, call for facilities that are well-suited for the challenges of these operating conditions. Techniques such as supercritical fluid chromatography (SFC) or chiral separation also require specialized capabilities that may not be available at every manufacturing site. Recognizing these factors early reduces the risk of selecting a site that cannot accommodate the process as it is designed.

These reasons and more are why analytical and process development cannot be treated as separate activities. Like a choreographed dance, one misstep can trigger a chain reaction of disruptive and costly consequences. If the two groups are aligned, they can interact and pivot in real time, allowing analytical findings to inform process development as the project evolves.

Aligning Analytical Development with Process Evolution

As these choices shape the process, analytical development must evolve with it to accurately characterize their impact and establish the appropriate controls. Methods designed to support the need for speed may not support later specifications for key raw materials, in-process controls, intermediates and the final product. The time required to validate those methods should also be considered, as full method validation often takes longer than teams anticipate, which can eventually affect project timelines.

Impurity understanding is also important as the program advances and specifications are set. While full structural elucidation and synthesis of impurities can wait until the program progresses, it is critical to understand what these impurities are and the levels at which they are present. This will help with setting specifications early and deciding on control strategies as needed.

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Lessons From an Early-Phase Program

The experience of one early-phase biotech demonstrates how decisions made for an immediate need can impact development later. The company had produced a highly purified lot for toxicology studies using column chromatography. Although the approach was successful for achieving the target purity at that time, it inadvertently established strict drug substance specifications while providing insufficient toxicology coverage for several process impurities.

When the company approached Cambrex for clinical manufacturing, those specifications still had to be met, but column chromatography was not feasible for reaching the required purity at a larger scale. The Cambrex team was able to optimize the process by adding multiple crystallizations as purification points for intermediates, which eliminated the need for chromatography of the drug substance. This allowed Cambrex to consistently deliver API that met the existing specifications. Getting there, however, required additional process work with both financial and timeline implications.

Recognizing these potential consequences before they become limitations when the stakes — and the costs — are higher is critical for emerging companies without the resources to learn these lessons through experience. Leveraging that insight, though, is only valuable if it happens before potential issues become embedded in the process, raising another important question for early-stage teams: When should an experienced development and manufacturing partner become involved?

Why Timing Matters in Your Outsourcing Strategy

Ideally, CDMO engagement takes place after route scouting and before process development starts in earnest. This gives them an opportunity to review and evaluate the process and parameters before they are finalized; conversely, bringing in an outsourcing partner after this point will limit their ability to make meaningful improvements. There is also enough information at this stage for the CDMO to evaluate manufacturing considerations and determine whether its capabilities align with both current and future needs.

This does not mean asking a CDMO to design a commercial process before the molecule has demonstrated its potential. Phase-appropriate development remains essential to balancing scientific rigor with speed and investment throughout the path to commercialization. The objective is to introduce manufacturing-informed expertise into the program at a point when it can still influence key development decisions.

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Keeping Today's Needs and Tomorrow's Priorities in Sync

Early development will always require teams to make decisions amid some degree of uncertainty. Phase-appropriate development helps lower risks and cost by preventing teams from investing in work that is not yet warranted. However, the key to success lies in the ability to recognize the aspects of development that impact only the immediate milestone and those with the potential to carry significant consequences into later phases. The route of synthesis, raw material selection, synthesis operations, analytical strategy and impurity understanding are closely



connected areas where information gained in one can affect what is required in another.

Bringing experienced development and manufacturing perspectives in early allows teams to respond appropriately as new information emerges while keeping today's decisions aligned with tomorrow's priorities. Like any well-choreographed performance, success does not rely on every move unfolding exactly as expected; it depends on making each one with an understanding of where it needs to lead.



About the contributor

Swaroop Mathen, Senior Director, Chemical Development, Cambrex High Point

Swaroop Mathen received his Ph.D. in Organic Chemistry in 2002 from the Regional Research Laboratory (currently NIIST, CSIR), Trivandrum, India, under the direction of Professor Vijay Nair. Swaroop had two years' experience at AMRI prior to joining Cambrex High Point in 2004.