WHITE PAPER

Accelerated API manufacturing by combining early-stage and late-stage process development

Manufacturing phase 1 clinical material in as little as 12–16 months

Traditionally, early-stage and late-stage process development have been done separately, with early-stage mostly focused on material production and late-stage on process intensification. As more molecules in development fall under an orphan or fast-track indication, the traditional approach of linear development stages can be counterproductive—not to mention expensive—due to investing resources in perfecting a process prior to early clinical phase success. Addressing some of the aspects of late-stage process development during the initial process development can help save valuable time following phase 1 clinical studies.

The pharmaceutical industry has changed in the past few years with some small molecule drug products being brought to market a short time after discovery. Fast-track and orphan indication drugs, as well as high-potency oncology drugs, are generally low-volume, high-value, patient-impactful medications for which accelerated timelines and expedited market entry equal success. In fact, fast-track drug substances progress from early-phase clinical studies to commercialization in about one-third the time of other small molecule drugs. This has put pressure on drug companies and their CDMO partners to produce phase 1 material in as little as 12–16 months depending on the complexity of the molecule.

But how to get that early drug substance in such a short time span? This white paper describes what to consider during early-stage development to avoid some of the common pitfalls and speed up the progression from molecule to market.

Seven considerations when combining early- and late-stage process development for fast-track drugs

Traditionally, pharma companies have expected a CDMO to develop a process for discovery through commercialization in stages, and this would take several years. If a typical drug development cycle lasts between seven and 10 years, the early stage can take two to four years. During this time the focus is on making a few kilograms of the drug substance, enough to support early toxicological work and phase 1 clinical studies while ensuring quality, safety and reproducibility. This leaves other considerations, like cost, optimization of unit operations and process validation, until later stages of development. Startups and large companies depend on timely completion of early-stage synthetic route development and characterization, ideally leading to promising results in phase 1 trials, to secure additional external or internal investment for second- and third-generation process development, as well as for the move to commercialization.

"What differentiates Curia is our ability to quickly adapt to the needs of the small molecule API market. Depending on the complexity of the molecule, our goal is to produce GMP material for our client's first clinical batch in 12–16 months."

— Jamie Grabowski
Vice President, Portfolio and Sourcing

It can be hard to convince a customer with a potential drug to see the value in considering late-stage process development during this early stage. Laying out the foundation for a good process, and addressing proactively some of the common challenges that one encounters at later stages, gives confidence to the customer that there is a scientifically sound process that can be easily built upon in manufacturing.

Designing our synthetic scheme and experimental layout during early stages provides high-quality and complete data. This minimizes the need to reproduce many of these experiments at a later stage, thereby reducing costs and increasing efficiency and the likelihood of manufacturing success during scale-up.

Using tools such as Design of Experiments can quickly identify those factors that have an impact on critical quality attributes (CQA). A close watch on engineering considerations for unit operations, such as phase separations, filtration times and drying times can significantly reduce optimization times at a later stage.

Data organization also contributes to efficiency. As analytical methods are tweaked or redeveloped during the course of process improvements, comparison to older data becomes critical. Companies planning and executing this way require an experienced team to support them in seven key areas.

1. REACH FOR LOW-HANGING FRUIT DURING EARLY-STAGE PROCESS DEVELOPMENT

In most cases, material production during early-stage development trumps developing an optimized process. Although the focus at this stage largely lies around the quality of the drug substance and the safety and reproducibility of the process, look out for opportunities regarding the quality, availability and supply chain details of the materials selected.

2. OPTIMIZE ROUTE OF SYNTHESIS

The medicinal chemistry route sets the foundation for early development and it is essential to optimize your synthetic route early. It's typical to freeze the synthesis prior to late-stage process development—changes to the route are time-consuming, expensive and, in many cases, involve new bridging toxicological studies due to changes in impurity profile. Settling on the right synthesis helps avoid some common issues, including:

- A linear synthetic route that lacks convergence
- Oily intermediates
- Late chiral resolutions
- Inefficient atom economy
- Extreme reaction conditions
- Hazardous materials
- Purifications by column chromatography
- Use of heavy metals towards the end of the synthesis
- Toxic solvents

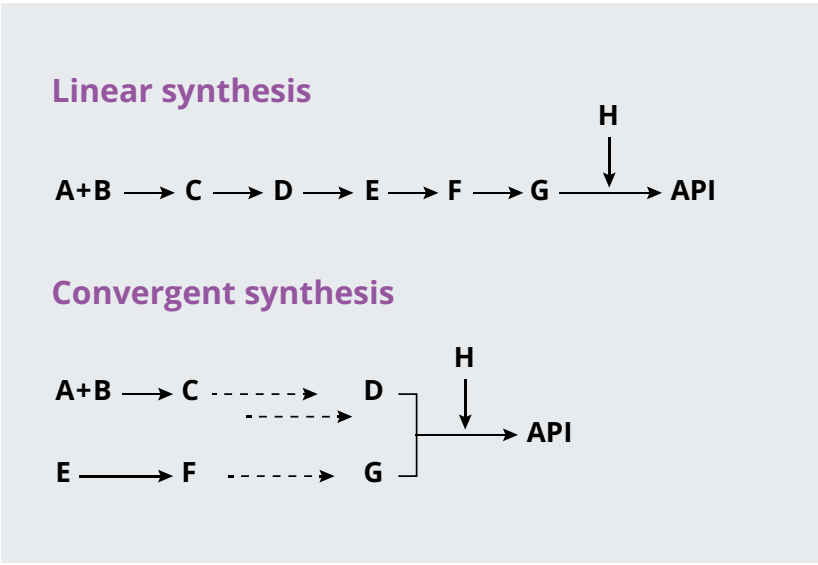
These issues will quickly jeopardize the ability to meet material supply needs as demand increases during clinical studies and commercialization. Capacity constraints and scheduling conflicts during rapid scale-up further add to the woes of an inefficient and lengthy synthesis.

The benefits of convergent synthesis

A linear synthetic route has the disadvantage of being more expensive, less efficient and riskier (Figure 1). For example, if a linear synthesis has 20 steps, and something goes wrong towards the end, the entire batch is lost. Instead, convergent synthesis can include parallel synthesis of two (or more) intermediates (e.g., D and G in Figure 1), possibly at different facilities and in different countries. Not only does this speed up the synthesis but, if an accident happens to one reagent (e.g., D), only that reagent needs to be remade. The other reagent (e.g., G) has not been affected.

These intermediates can then be brought together to make the API. In most cases, such intermediates could be designated as regulatory starting materials carried out under non-GMP conditions and with adequate release criteria could be used in the final assembly. This is more efficient and less risky than linear synthesis.

Figure 1.
A comparison of linear and convergent synthesis



3. ESTABLISH THE FINAL PHYSICAL FORM

The final physical form, or polymorph, is the solid-state property of the API. Polymorphisms affect the absorption, bioavailability and pharmacokinetics of the drug and have been a big issue in the industry for the past 25 years. Deciding on the physical form of your API and intermediates prior to the first clinical batch, and understanding the polymorph landscape, helps develop a confident process; it also creates a more valuable product by identifying and capturing the intellectual property (IP) that surrounds the most desired polymorph.

It is important to identify the most appropriate physical form for the API and intermediates early. A systematic salt screen followed by a polymorph screen leads to the most desired solid form based on solubility, crystallinity, hygroscopicity and shelf stability. Choosing an amorphous form or metastable form is not uncommon, but detailed understanding of the solid form at the various stages of development becomes crucial in developing a process for large-scale production. Intermediate solid form changes can also lead to issues during isolation, such as extended production time or changes in impurity profiles, impacting quality and solubility in subsequent reactions. Consulting with an experienced IP team could avoid manufacturing issues at any scale, and developing an IP strategy early could dramatically increase the value of the compound of interest.

4. REGULATORY STARTING MATERIALS (RSM)

The core structure of the API is made up of commonly accepted fragments, or RSMs (e.g., D and G, Figure 1). RSMs are chosen so that an adequate number of steps are executed under GMP conditions that demonstrate complete control over the API quality. Nonetheless, it is common to avoid excessive steps under GMP during early-stage production and extend synthetic steps further downstream. This approach provides flexibility to make advanced intermediates under non-GMP conditions with minimal analytical and quality concerns leading up to the synthesis of RSMs. Early consultation with an experienced regulatory team is essential to justify and display control of quality within the process.

5. AUTOMATION FOR ENHANCED DATA COLLECTION

Emerging technologies and equipment that facilitate data collection while minimizing the number of experiments must be deployed as quickly as possible to accelerate process development and shrink the timeline to meet the aggressive demand for material. Use of automated technology helps in reliable, reproducible and retrievable data that can help make important changes in the process. Here are some of the tools that can speed up development.

Process analytical technology (PAT)

PAT is used to develop processes with inline data information, which drastically improves the speed of developing a process. It gives insights to reaction mechanisms and pathways that permit educated changes rather than changing one parameter at a time. React IR, *in situ* Raman, FBRM, turbidity, pH probes and the various other automated tools assist in developing data-driven changes to reaction conditions, crystallizations and other unit operations. Similarly, use of these tools in manufacturing can provide real-time data and the means to operate under tight parameter limits.

Artificial intelligence (AI) and reaction predictability

AI is gaining attention for its use in developing synthesis and process optimization. The outcome of reaction from a library of reaction conditions can be predicted with good accuracy. Modern tools associated with AI capabilities can become a powerful tool to drastically reduce the overall time needed for process development. Some of the current uses for AI include:

- Predicting the outcome of scale-up batches.
- Understanding reaction outcomes and minimize the number of reactions that need to be carried out in the lab.
- Speeding up simulation and modeling work. When coupled with lab automation, AI increases the predictive power of these tools.
- Computer-aided drug design (CADD) to help with medicinal chemistry and the design and discovery of promising molecules.

6. LEVERAGE IN-HOUSE ANALYSIS

A strong analytical team working in tandem with process development experts provides timely and reliable analytical information to make critical directional changes to the process. Dedicated analytical expertise in-house, along with the availability of all the necessary equipment, limits outsourcing needs and minimizes time required. Having a strong analytical group supporting the process development engineers is one of the most critical factors in shrinking the overall timelines of a project.

7. EFFECTIVE TECHNOLOGY TRANSFER

Effective technology transfer is vital to the success of early-stage process development. A well-established and effective means of relaying all information—not just technical documents, but the entire process information and all the critical parameters—is vital to avoid errors and misunderstandings. It's no surprise that a second batch produced in a manufacturing suite has a higher success rate than the first scale-up batch. A successful tech transfer requires:

- Effective information transfer
- Early involvement of engineers and the technical services team
- Development of a process built to run in existing equipment
- Presence of the process chemist on the floor during early batches

Late-stage development to commercialization

Once some batch history is established and the process moves towards registration, process understanding of unit operations and a meticulous evaluation of all parameters is warranted. The initial judgment and design of the synthetic route becomes meaningful as cost of goods and sourcing become important. With increasing scale, logistics and risk considerations take higher precedence, while technical details such as optimal unit operations, hazard assessment and throughput remain relevant. Control strategies and contingency plans play a vital role for maintaining steady production of your API.

Late-stage process development and validation focus on:

- Intensification
- Edge of failure
- CQAs
- Reproducibility
- Economics
- Cost of materials
- Simplicity of workup

Establishing batch history

Chemical process development is iterative, and the CDMO needs to establish sufficient batch history to ensure confidence in execution at scale. It is imperative that the process chemist be present on the floor at all times during the first few production batches. Some things to watch for during this stage:

- Engineering and processing issues arising from heat and mass transfer can manifest during multiple runs.
- A new polymorph can develop during production.
- Deviations in the first few scaled batches can provide insights into the process. These will be used in the development lab to iterate a successful campaign.

Validation

Validation requires an understanding of all the unit operations and optimizing each part of the process. A process needs to be validated to ensure it is robust, reproducible and delivers consistent quality. Aspects of the validation include:

- Mapping out the design space for a process in keeping with quality by design.
- Identifying the critical process parameters and developing a control strategy so the process consistently meets CQAs.
- Fate and purge data is used to set specifications for commercial batches and provide justifications for deviations in commercial batches.

A validation summary report forms the basis for the CMC section of an NDA.

When it comes to speed, integrated process development counts

Partnering with a CDMO that has the experience to consider aspects of all stages of process development from drug discovery to commercialization has been proven to increase the speed of bringing a small molecule to market.

Want to learn how Curia can smooth the path to market of your next API? Visit curiaglobal.com/research-development/development.

ABOUT CURIA

Curia is a global contract research, development, and manufacturing organization (CDMO) with over 30 years of experience. With an integrated network of 20+ facilities worldwide and a team of 3,000+ dedicated professionals, we specialize in partnering with biopharmaceutical customers to bring life changing therapies to market. Our offerings in small molecules, generic APIs, and biologics span discovery through commercialization, with integrated regulatory, analytical, and sterile fill-finish capabilities. Our scientific and process experts, along with our regulatory-compliant facilities, deliver a best-in-class experience across drug substance and drug product manufacturing. From curiosity to cure, we are your trusted ally in accelerating life-changing therapeutics.

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