SOLVED WITH
SOLIDARITY & SCALE

WHITEPAPER

Manufacturing process scale-up for Phase III: Clear sailing or storms ahead?

Sanjay Konagurthu, PhD

Senior Director, Science and Innovation, Thermo Fisher Scientific

John W. Burke

Senior Manager, Manufacturing Sciences, Thermo Fisher Scientific

• API • BIOLOGICS • VIRAL VECTOR SERVICES • EARLY & LATE PHASE DEVELOPMENT • CLINICAL TRIAL SOLUTIONS • LOGISTICS SERVICES • COMMERCIAL MANUFACTURING

patheon

Abstract

Your compound has been progressing well through small-scale studies. The data collected in early trials suggest the formulation is safe and has great potential for improving its intended target condition. Critical make-or-break Phase III studies are on the horizon to demonstrate safety and efficacy in large numbers of patients.

Is your team ready to manufacture larger batch sizes to support this endeavor? Possibly.

Regardless of whether your group has been diligently planning for scale-up since Phase I or you have delayed scale-up work until now, it would be a mistake to assume Phase III will be clear sailing. The reality is that several manufacturability problems could be brewing that will rain down during Phase III and cause costly delays, no matter how skilled the product and process development teams may be.

Here's a look at some factors that pharmaceutical companies of all sizes and experience levels must consider to ensure their formulations are successful during larger-scale manufacturing.

The three pillars of success

Drug formulators need to be mindful of a compound's performance, stability and manufacturability from the get-go and throughout formulation and process development for large production batches to run smoothly. While drug product development scientists commonly work on formulation development and stability improvement in the early Phases I and II of a drug product, manufacturability is not always a priority. What they don't realize, however, is that scale-up is not always trivial or predictable unless process knowledge is developed that is scale-independent. This knowledge should guide equipment selection, link the critical process parameters (CPPs) to critical quality attributes (CQAs) and establish the design space (DS). Sound scientific/engineering principles and mechanistic models should be employed whenever possible for scale-up of pharmaceutical unit operations. In addition, a robust risk-assessment program invoking Quality by Design (QbD) principles at each stage of development is critical for successful scale-up.

Drug formulators need to be mindful of a compound's performance, stability and manufacturability from the get-go and throughout formulation and process development for large production batches to run smoothly.

When formulations are ready to be manufactured on a larger scale, the necessary equipment for producing larger batch sizes inevitably changes. While the apparatuses may seem similar—just larger—they often are quite different. Additionally, for various reasons, the equipment design/manufacturer may be quite different when transferring from development to commercial scale (e.g., encapsulation or coating unit operations).

Thus, transferring the results R&D obtained on laboratory scale to the pilot plant and finally to production scale can be challenging. Without a thorough understanding of process scale-up, larger scale equipment can impact a formulation's components completely differently than small-scale equipment might. This change in scale can alter a formulation's manufacturability and problems can become evident or magnified in certain projects.

Change in scale can alter a formulation's manufactur-ability and problems can become evident or magnified in certain projects.

Unexpected surprises

What are some common pitfalls that developers face during scale-up? What follows are several examples of problems that frequently surface as developers advance into later-stage development.

Blending challenges. On the solids side, physical interactions between powder components at larger scale can cause numerous issues. With a typical unit operation such as powder blending, for instance, common problems develop while attempting to scale from one geometry to another (e.g., V-blender to a bin blender), varying fill levels at different scales and keeping blending times constant while changing the blender speed. Process analytical technology (PAT) tools for monitoring blend uniformity are helpful during development and scale-up.

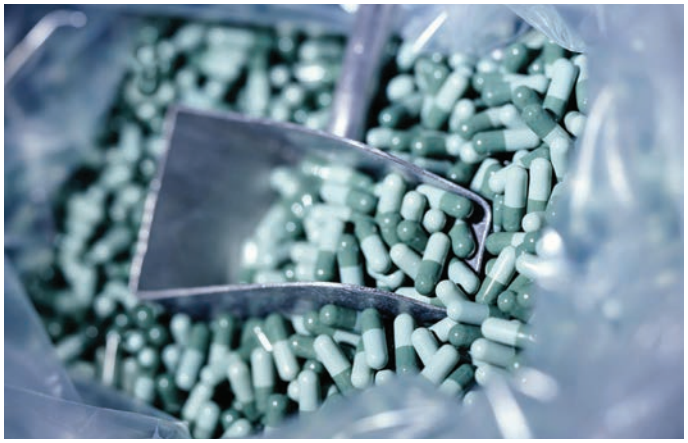
Segregation is also a major concern for product uniformity caused by poor or incomplete blending. The flow behavior in bins and hoppers is key for understanding segregation tendencies as scale-up activities occur. Understanding the mechanisms of segregation and controlling the segregation phenomena during powder handling and transfer is critical to producing a uniform product.

Granulation. Granulation processes are widely used for powder densification to improve the product content uniformity and flow properties. Common approaches include wet granulation (e.g., high shear, fluid-bed) and dry granulation (e.g., roller compaction) processes. Depending on the approach used, the scale-up process development strategy from the lab- to pilot- to commercial-scale needs to be understood. The mechanism of granule formation for these wet and dry granulation processes are very different and must be understood at a particulate level for each approach. Then, the appropriate process control strategy, in-process testing, available PAT tools and end-point detection should help in guiding the scale-up strategy.

Tableting. For tableting applications, the process scale-up involves different speeds of production in the same die-cavity. As tablet formulations are moved from small-scale research presses to high-speed machines, potential scale-up problems can be eliminated by simulating production conditions in the formulation development lab. A formulator can learn a lot in the early stages of development by understanding the inter-play of the dynamics between the Compression Pressure–Tensile Strength–Solid Fraction relationship of the tablet dosage form. Invoking the use of compaction simulators or emulators can significantly help in de-risking transfer across different press designs and strain rate sensitivity/dwell time differences between development and production presses for formulations.

Coating. Another issue that might be problematic is the scale-up of spray coating processes such as fluid-bed or pan-coating processes, which have numerous process variables that are interdependent on one another. Developing the appropriate thermodynamic models of the coupled heat and mass-transfer that occurs in these unit operations is important for running simulations of the process. Focused Design of Experiments (DOE) targeting the CPPs, and linking the CQAs would help in mapping the DS efficiently. Thus, a combination of first principles mathematical modeling in conjunction with targeted experimental designs is a highly beneficial strategy for scale-up.

Fill-Finish. Hard-to-predict scale-up challenges can also surface in the development of sterile products, which can be time-consuming and expensive to correct—especially for freeze-dried products. The more information that formulators and process engineers can gather early in the game to help define the DS around the project, can help mitigate problems during the scale-up process. CPPs that are well defined and understood along with a well-defined quality target profile (QTP) help drive a smooth transition during scale-up activities. The cost of rework, in terms of both time and money, with a lyophilized product can lead to significant delays to timelines and to budgeting. The risk of neglecting to collect such data to support the DS and the QTP, using both traditional and newer techniques, can create a gap in knowledge that in the long view of the project can be very detrimental.



Furthermore, when it is time to scale-up a lyophilized process, both large and small pharma companies tend to neglect doing a true thermal analysis, which is problematic. We've seen countless times how a thorough thermal analysis—making use of tools like freeze-drying microscopy, differential scanning calorimetry and thermogravimetric analysis—can offer very detailed and valuable information about structural and behavioral changes in molecules associated with freeze drying. For some clients, a detailed thermal analysis has helped uncover that the product is not on target to achieve critical thermal properties of the formulation like glass transition (Tg) or collapse temperature (Tc) and would have melt-back issues if we didn't make some adjustments before moving forward.

Moreover, some firms blindly enter Phase III with no understanding of how vials (currently only filled in a slow or semi-manual process) will fill at high speeds. If clients have not completed stress studies about whether products are affected by shear or whether vials bubble out the top, for instance, they might be facing the possibility that the product could have a wide range of problems as they move to the commercial realm.

Building security into Phase III

How can firms limit unexpected surprises in Phase III?

In an ideal world, formulators working on early development projects would be keenly aware that every decision they make could have strong implications on a compound's successful scale-up potentially years down the road. Unfortunately, in the rush to market and with limited large-scale production experience, small and virtual companies often do not have the bandwidth to plan for the challenges that could arise in Phase III.

One of the most important things for companies to understand is that investing in scale-up in early phases can save dividends in the long run. At this stage, formulators and process engineers should obtain as much information as they can about what is happening at the mechanistic level of a formulation and process because it is much less expensive to identify and address manufacturability problems earlier in the process than later.

In addition, evaluating process development methods and critical process attributes helps mitigate scale-up problems. This QbD approach is expected from a regulatory point of view but also is advantageous to companies for saving time and money redoing process development work. The famous quote from Leo Baekeland, the inventor of Bakelite, the first synthetic plastic, aptly applies here: "Commit your blunders on a small scale and make your profits on a large scale."

A well thought-out scalability approach throughout a compound's development will set the stage for successful Phase III scale-up, though it will never be entirely predictable. That's why late-stage transfer to a knowledgeable CDMO can also be an important tool for building further assurances of success into the process.

One of the most important things for companies to understand is that investing in scale-up in early phases can save dividends in the long run.

A knowledgeable CDMO partner can help bolster product knowledge in Phase III during a rigorous technical transfer process and with risk assessments to identify potential shortfalls before manufacturing (and potentially failing) at large scale. This approach has the dual-pronged benefit of also collecting sufficient data to show regulators that a process is robust enough to handle the many changes that could surface in commercialization.

This is key because many firms do not start thinking about QbD principles in early development stages, but it becomes critical to get the DS mapped out in the later stages. When clients partner with a CDMO that is well versed in how to apply QbD principles—especially in Phase III—the groundwork is laid for regulatory success. Centers of focus should include identifying CPPs, CQAs and process control strategies.

In addition to helping build QbD into a product, an experienced CDMO will have hands-on experience with a host of compounds in Phase III and thus will have deep knowledge to draw on for addressing problems that arise with specific manufacturing challenges in late-stage development. All these efforts—resulting from a detailed tech transfer to an upper-tier CDMO—will put developers in a good place to support their critical process validation efforts.

Summary

Some drug developers diligently design scalability into their formulations from day one and are fully prepared for larger-scale production during Phase III. Essentially, their only remaining task in preparation for full-scale manufacturing is to file the necessary regulatory paperwork and move forward.

Unfortunately, more often than not, problems inevitably surface in Phase III that can be difficult to predict, regardless of whether the project involves tablets, vials or another delivery format. Building scalability into a formulation throughout its development as well as transferring the project to a knowledgeable CDMO in Phase III can help mitigate some of those challenges.

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 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. 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.

Sanjay Konagurthu, PhD

Senior Director, Science and Innovation, Thermo Fisher Scientific

Sanjay has over 22 years of experience managing the development of drug compounds from the discovery interface through clinical and commercial manufacturing. His expertise spans a broad spectrum of therapeutic areas involving predictive modeling, formulation and process development of platform oral drug delivery technologies such as solubility enhancement and modified release. He has worked on a broad range of new chemical entities (NCEs) as well as the lifecycle management of marketed products. He has eight patent and patent applications and is the author or co-author of more than 40 publications, posters and webinars. Dr. Konagurthu earned his Bachelor of Technology degree from the Indian Institute of Technology (IIT), Madras, and his PhD from the University of Colorado in Boulder, both in Chemical Engineering.

John W. Burke

Senior Manager, Manufacturing Sciences, Thermo Fisher Scientific

John has over 20 years of experience in the pharmaceutical arena. His experience includes analytical development, formulation development, technical transfer and manufacturing support. He leads a group of eight scientists at Thermo Fisher's site in Greenville, North Carolina, facilitating the development and technical transfer of pharmaceuticals through all phases of development. John started his pharmaceutical career in the analytical laboratory, supporting a wide range of products and testing techniques. His laboratory experience includes raw material testing, flame atomic adsorption, GC, and HPLC. He transitioned into formulation development, supporting both NDA and ANDA programs for parenteral and lyophilized products. He successfully transferred multiple projects to both internal and external manufacturing facilities. John holds a BS in Chemistry from Pfeiffer University, and completed his Masters in Chemistry at the University of North Carolina in Wilmington, where he synthesized multiple salts using a model drug and evaluated the effects of the new salts on lyophilization cake characteristics.

+1 919 226 3200 • thermofisher.com/patheon • pharmaservices@thermofisher.com

Published 07/21

ThermoFisher SCIENTIFIC