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The Race to Phase III: A Cautionary Tale of Scalability

As drug products move from preclinical through Phase IV development stages, clinical material demand grows tremendously. Production scale-up is rarely straightforward. Scaling up drug product manufacturing often requires time-consuming, expensive and unexpected challenge resolution.

How can firms mitigate risks and make scalability as smooth as possible? In this representative example, we follow the paths of two companies facing this challenge as they learn how a science-led, risk-based development approach yields a more successful outcome in the long run.

Goal: Fast-Track Approval

Company A and Company B are working on new chemical entities for an oncology indication in a therapeutic category of an unmet need. These potentially life-saving medications are on fast-track timelines for regulatory approval, and both firms want to get the molecule formulated into coated tablets as quickly as possible. Given the abbreviated timelines, neither company has the luxury of time. Getting scale-up right the first time is an absolute "must."

Early Work: Fact-Finding Mission

Ballpark the dose

To avoid repeat work down the road, Company A decides it must have a good idea of the clinical dose fairly quickly. This is easier said than done. Early trials verify a product's safety and tolerability in animals using significantly higher doses than are usually appropriate for humans. Once those data are available, developers can start estimating a clinical dose. To collect data at both ends of the dosage spectrum, early-stage formulations must be flexible.

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Company A determines that a high dose is the best format for its molecule and now needs to learn which API properties might affect the development process. Company B has a highly potent API delivered in a low dose. These types of formulas are at risk of content uniformity problems, which Company B decides to investigate later.

Characterizing the API

Company A assesses the molecule's solubility and finds that it is has good solubility, which is positive news because no solubility enhancement techniques are needed. At this point, Company A works to understand as much as it can about the API's physical and chemical properties (e.g., particle size, particle shape and flowability).

Company B does some basic studies but decides to accelerate the development and wait until later in the process to do full characterization work.

Target product profile

With information in-hand about its API, Company A starts finalizing a clear target product profile that will guide future work and ensure the project remains on track to meet its initial goals. Such information includes patient population, the route of administration, dosage form and amount, indications, product specifications and other key attributes. Company A is clear about these expectations, knowing major change down the road could send them back to the process development drawing board.

Company A's information-gathering process is not inconsequential. It contributes to the strong foundation that a robust formula and process must have for regulatory success. A smart scalability approach is like building a structure layer by layer. Without collecting enough information early on, the entire process may eventually crumble as it cannot sustain the rigors of high-speed production. The subsequent steps needed to build the process will be on shaky ground—and the entire process may crumble later on as it cannot sustain the rigors of high-speed production. Laying a strong groundwork of process knowledge helps Company A not only prepare for its immediate next steps of formulation work, but also for the scale-up techniques that will be used for scale-up about a year down the road.

The competitor, Company B, is focused just on getting to proof of principle and decides that a market-like target product profile really is not needed at this point, and intends to fine-tune the profile when the time comes in later phases.

A Stitch in Time…

Do I *really* need a risk assessment?

To save on time and money, Company B chooses a small CDMO with immediate capacity and quickly starts manufacturing material for first-in-human trials. While a couple of batches do not compact

perfectly and some friability issues are apparent, Company B moves forward with whatever product is usable. Even though the company has not completed much process development work, the developers feel delaying this effort is the only way to meet its tight timelines. If necessary, the company will modify the process and formula down the road. Unfortunately, Company B does not realize that it is setting itself up for considerable re-formulation time by not addressing the product performance issues. When companies neglect this testing, it is not uncommon for them to reformulate compounds dozens of times over several years without success.

Company A is guided by its CDMO (a larger, single-source manufacturer) to conduct a simple early phase-appropriate risk assessment during tech transfer. At Patheon, we often find that this work not only generates a better understanding of the molecule's chemical and physical properties, but also identifies the risks that guide excipient selections and process recommendations while keeping a close eye on critical processing parameters. If we uncover an unusual property, we might recommend additional testing to learn more.

In this example, the risk assessment reveals that Company A's molecule is unstable in water. This information prompts the CDMO to begin thinking early on about the granulation method for later stages: Is wet granulation still a possibility or should dry granulation be used to reduce risk?

Meanwhile, Company B's approach is faster and cheaper, but carries more risk into the later stages of development because they do not know whether the formulation is robust. Producing a tablet at a small scale is relatively easy, but larger scale work is a completely different ballgame. Finding this out the hard way close to commercialization can be a catastrophic mistake.

Early scale-up strategy

With the risk assessment pinpointing a clear experimental path for formulation and process work, Company A's standard process development activities begin. At Patheon, we feel strongly that early development is a critical time for ensuring the process can be replicated on a larger scale.

Company A's CDMO recommends they complete some additional tests to fully understand the API's properties, which will help avoid some hiccups later in the process. For example, understanding more about the compaction properties of Company A's API ensures the formulation can compact successfully on a slow small-scale press as well as a high-speed commercial press.

At Patheon, we often run a compaction simulation to help ensure success on a high-speed press. Simulation can also help us smooth out road bumps in many areas. If wet granulation is being used, for instance, we can input variables such as water amount to predict its effect on the formulation's robustness.

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Company B skips the assessment process, with Phase I going pretty well; some borderline bioavailability, solubility and tableting problems are flagged, which the company thinks will sort itself out in larger batch manufacturing trials. It advises its CDMO to start producing quantities for its Phase III work.

Another risk assessment?

Company A has decided on dry granulation. The CDMO advises that additional risk assessments will help increase the chance of a successful transition to later-stage clinical supply demands.

At this point, it's key to know whether any scale-up risks remain unaddressed. This work starts to fall under the Quality by Design (QbD) directive by assessing the robustness of the formulation and the process, and seeing how the steps are interwoven. The output of this risk assessment provides: a) confidence that a company can scale-up and b) an outline of the experimental plan to follow during scale-up.

What goes into risk assessments is knowledge gained during development. This step-by-step scale-up strategy makes a good case for why Company A chose a CDMO that can do early

through late-phase work plus commercialization. All knowledge for successful full-scale manufacturing is captured within one organization and provides strong layers of process knowledge, building quality into the process design from the get-go.

Phase II hiccups

Company B determines in Phase II that variable bioavailability is a major problem. The company goes back, repeats some lab work, conducts additional clinical tests and corrects the problem. This causes an eight-month delay and an additional investment the company did not intend to spend repeating necessary rework on formulation and process development activities. This includes a new Phase I trial, which according to a 2014 US Department of Health and Human Services report, will cost another $4 million. Additional attempts at a Phase I trial will add $5 million to Company B's R&D costs.

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The company hopes that scale-up will be easier the second time around.

Larger-Scale Work

Company A needs a larger quantity of clinical supply as the molecule progresses into Phase III. The CDMO analyzes the formulation and process development reports for completeness and then defines the scale-up strategy. There's a clear correlation between the critical process parameters and material attributes as these relate to the critical quality attributes (CQAs).

A response surface design study begins to gain mechanistic understanding of the process. Pre-evaluation batches are made to provide more confidence going into process performance qualification.

The CDMO also moves to finalize a validation strategy, which is based on early-scale development work. Because Company A has gained significant process understanding throughout the development process, the CDMO believes just one or two validation batches are needed and is confident that the process will pass regulatory scrutiny.

At Patheon, we often find if a company has a good process understanding (and a well-defined strategy for getting there) for scale-up, it may not need to submit data on three validation batches—saving even more time and resources.

Company B brings its molecule to a larger CDMO with the hopes of jumping back into Phase II/III. Unfortunately, initial assessments during tech transfer reveal there are fundamental problems, and a great deal of characterization work is needed before the formulation can be tableted at high speeds. Facing the possibility of additional time and money needed to make the API work, Company B decides to suspend work until it can figure out how to move forward.

Summary

When aggressive timelines are a "must," it's critical that companies don't gloss over early-phase scale-up throughout the development process. The time and effort spent on risk assessments and thinking about scalability early on will pay dividends in the long run as the path toward regulatory approval is smoother.

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Published 09/17 PATH0710