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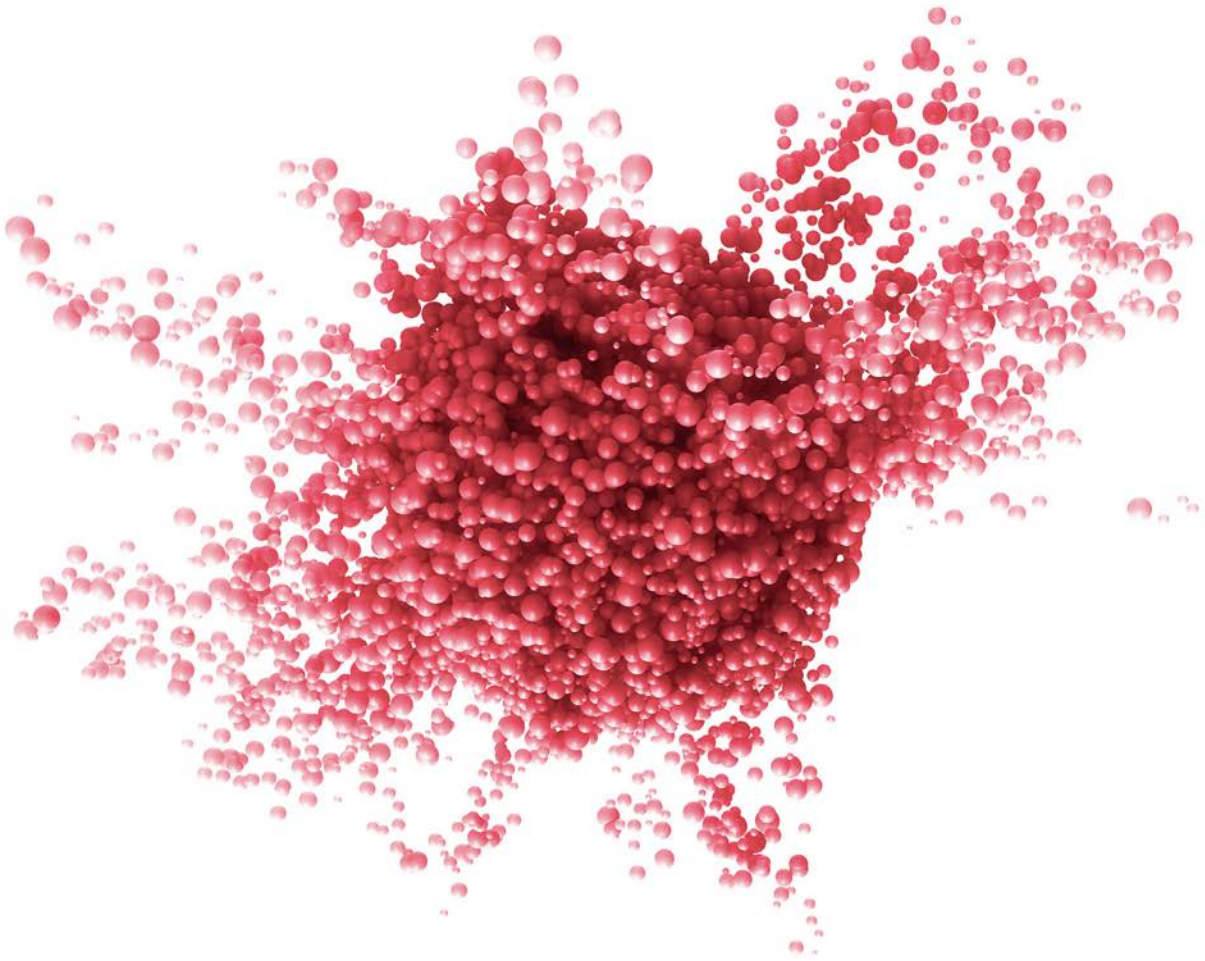

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What you need to know to avoid costly delays in your API scale-up

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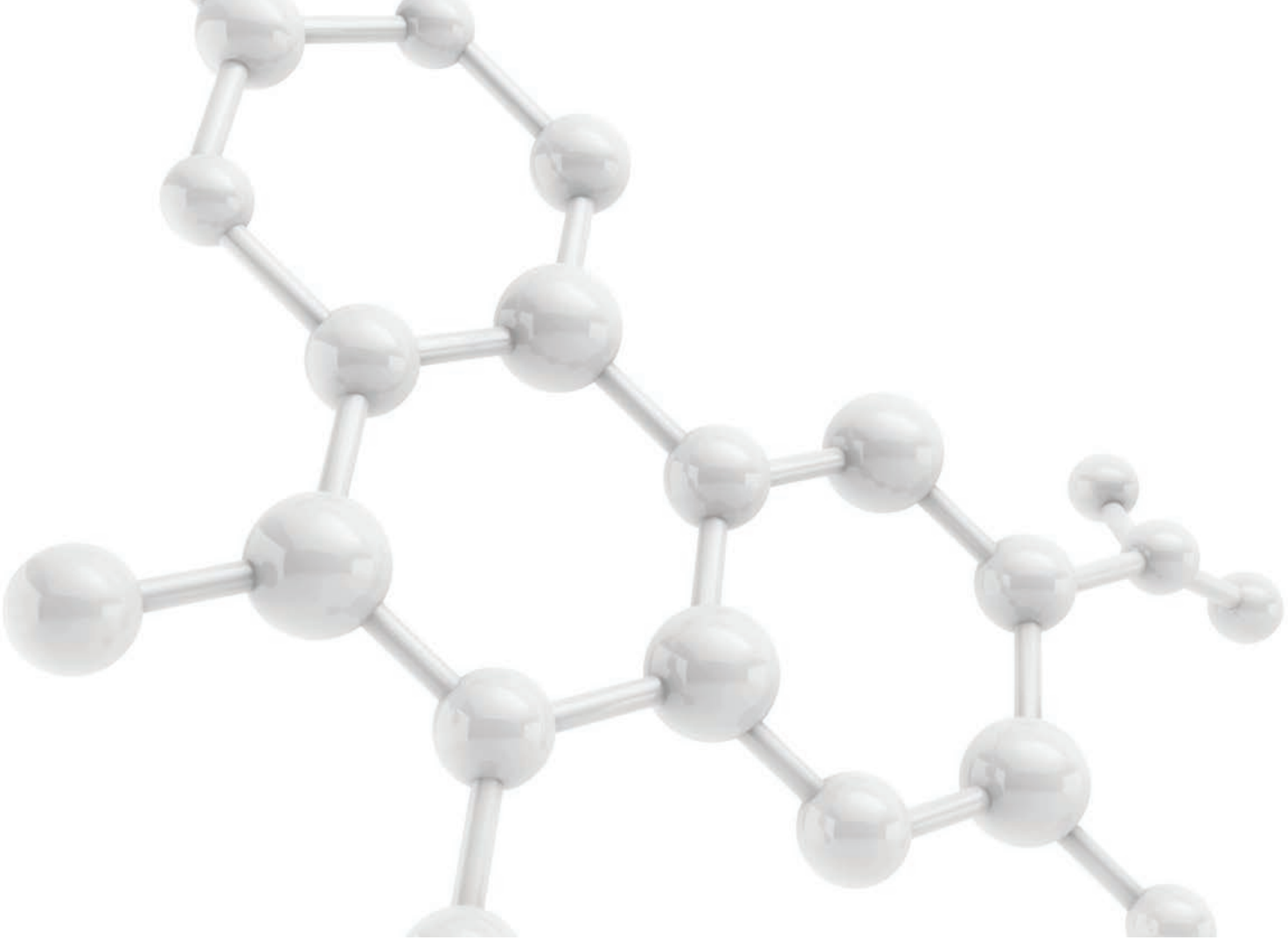

Abstract

Traditionally, the development of a small-scale synthesis for an active pharmaceutical ingredient (API) and its scale-up to meet the materials demand for clinical trial phases is a sequential activity that passes through multiple sets of hands. The developer must be prepared to encounter and react to any changes to the API's quality attributes—such as by-product profile and physical form—even if the synthesis used at a small scale is the same one used at a large scale. If undesirable effects occur during the development process that negatively impact API scale-up, it can prevent a company from delivering a product with reliable quality and efficacy. For these reasons, a company must be aware of any potential conditions that could occur at a small-scale that could create major issues during commercial scale-up.

The challenge of unlike minds

In the early stages of drug development, the focus of a chemist developing new compounds is more on efficacy and much less on convenient production. After achieving efficacy, that "recipe" is passed on to a team of chemists, process engineers, and analytical experts. This team of experts must develop an acceptable synthesis route that efficiently produces the same result on a commercial scale as it did in the laboratory.

Depending on the unit operation, this task can become extremely difficult and time-consuming. There are process features that should be kept constant with scale, e.g. mixing times, reagent addition times, and reaction times; yet, they usually change, as a vessel with fiftyfold volume does not provide fiftyfold heating/cooling surface.

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Its stirrer also may not mix as fast as a stirrer at lab-scale. Other process features may not change linearly, either. Thus, a fiftyfold increase in scale may lead to unforeseeable effects on yield, product quality, and by-product profile. Examples of processing steps that can create challenges in scale-up are those that include chemical reactions:

In different phases—this includes processing steps involving liquid/liquid mixtures, such as biphasic reactions or extractions, which may show pronounced scale-up effects caused by transport phenomena. Similarly, operations involving solid/liquid mixtures, where solids are dissolved, precipitated, or separated from a liquid may show pronounced scale-up effects; crystals created during this step on large-scale might have properties that are different from those crystals created during the small-scale process for a variety of reasons.

With hazardous reagents—many synthesis routes devised by medicinal chemists make use of efficient yet hazardous reagents. Using these reagents at a large scale can create serious issues when it comes to the safe handling of these materials by a company and its employees. Also, many of these reagents react quickly and release considerable reaction heat. This poses problems during scale-up, as conventional API manufacturing equipment does not provide the required mixing rates and heat removal capacity.

The result is process changes, such as applying expensive cryogenic conditions or prolonged reagent addition times, that have unknown effects on product quality. In addition, the number of chemicals not allowed to be transported on a large scale is increasing. This creates a considerable risk of supply of starting material and/or reagents. If addressed early, a chemist can develop ways to circumvent those hazardous reagents or replace them with others.

If necessary, a company could produce them on site on an as-needed basis. To do this, a method would need to be developed that produces the hazardous agent from less hazardous precursors, so it can be consumed as it is created. For small companies, the resources necessary to do this may not be available. An alternative would be to team up with suppliers that have access to or possibilities of on-time/on-demand synthesis of those hazardous materials.

With high-quality/expensive materials—a company should be cognizant of the cost of the materials they are using, as they may be too expensive at a large scale or may not even be available in those volumes. Typical examples of such materials are certain advanced structurally complex homogeneous catalysts and chromatography materials. Catalysts may be well available at a laboratory scale but may not be manufactured in quantities needed for large-scale API manufacturing.

Process changes may become necessary to avoid the cost and uncertainties of using them. Likewise, chromatographic separations, while very efficient and frequently the method of choice for product purification on small-scale, may add significant cost, materials demand and development time if applied at a large scale.

While API synthesis is a small effort compared to the overall effort of finding a new drug substance, it requires a significant amount of time to synthesize an API, develop a formulation, complete clinical testing on it, and take it to market. Failing to consider any of the conditions above could result in a shortage in supply while a formulation is adjusted, thereby causing interruptions in a clinical trial that could put patients at risk.

Telling patients in need of a drug that they now have to wait for their medication is the last thing any company wants to do. This is why it is critical to have processes in place that can identify these reactions before there is a negative impact on a drug's development timeline.

A proactive approach to a reaction problem

To avoid problems caused by the issues outlined above as well as other scale-up challenges, a company should consider changing how it aligns the two unlike minds of chemists and process engineer. Instead of developing a synthesis and then passing it on only for issues to be recognized later, the two sides should work together simultaneously to address any obstacles as they are encountered. For example, a chemist develops the API at a very small scale and then shares it with the process engineer. The process engineer can then analyze it for any compatibility issues that might occur at a large scale, such as changes in product quality, by-product profile, raw material and plant costs, equipment availability, etc.

If any issues are discovered, the process engineer communicates them to the chemist. The chemist can then suggest alternative routes or modifications to make it scalable. This continues until a synthesis is developed that can be successful at a large scale. Some approaches a process engineer could use to discover these potential compatibility issues are:

Investigate the respective properties of the reaction mixtures early in development—Every process engineer will ask his chemist questions to determine if the kinetics and thermodynamics of a reaction can be scaled up. These questions can include:

- How quickly does it progress and how much heat does it consume or develop?
- Is the reaction mixture homogeneous?
- Can it be made homogeneous by a suitable solvent?
- How quickly do phases separate?
- How do the precipitates behave?

These are just some of the questions a process engineer can ask to ensure a large scale plant is designed to properly handle the respective reaction mixtures. While an exhaustive description is not required at this stage, early involvement such as this and a mutual understanding between chemists and process engineer can limit the risk of scale-up errors.

Establish the amount of waste a process will produce—Many small-scale syntheses use huge volumes of noxious solvents or large volumes of aqueous solutions containing contaminants that have to be removed or depleted prior to conventional waste water treatment.During scale-up, a company might strive to either recycle or replace those solvents with more benign solvents in order to reduce volume. Again, a clear picture on potential waste streams early in development gives direction to development and scale-up programs. Without this information, there is a risk of high disposal costs or even an inability to dispose of the required volumes of solvent.

The high attrition rate of drug candidates is frequently used as a reason to engage process engineer, and plant engineer too late in a drug development process. The effort of preparing a synthesis process for scale-up is comparatively small to the effort and time demand of late-stage changes that might require repeating earlier work or additional clinical trials.

Gather extensive data—Solubility, particle size and polymorpic forms are critical attributes that influence the pharmaceutical effect of a drug. This may depend on the formulation but it is critical to determine and consider these parameters early in development.

The benefits of continuous manufacturing for API scale-up

Batch chemistry is still the most widely used way of processing in the pharmaceutical industry, yet it renders many processes hard to scale. An alternative that has seen growing interest in recent years is continuous manufacturing. This approach has been extensively developed and used in base chemistry (e.g. refineries) and even in the food industry. It is based on the simple consideration that two volume elements of a reaction mixture will deliver exactly the same product if they experience exactly the same sequence of processing conditions. Instead of trying to achieve this by placing them in the same large scale reactor, where differences in processing conditions appear due to slow mixing and insufficient temperature control, these volumes are sequentially sent through a “flow reactor.”

While the “reaction time” is precisely defined by the “residence time” in the reactor—as it results from flow rate and reactor volume—the mixture may be exposed to any temperature, pressure, additional reagent in different parts of that reactor. In its simplest form, it is a channel (within a tube or a plate) with a heating/cooling jacket. Regulatory bodies, such as the FDA, have recognized the virtues of this processing concept as it allows superior control of process conditions and product quality.

With continuous manufacturing, a company’s production volume, which is determined by throughput and time of operation, can be quickly adjusted to meet the immediate actual demand. This is facilitated by an increasing number of suppliers offering ready-made or custom-made pieces of equipment. Any additional demand can then be met by prolonged operation and, if necessary, the construction of identical parallel plants.

More and more companies engaged in early development embark on this processing concept as it renders formerly hard-to-scale processes scalable and thus helps to avoid the process changes described above.

Despite its many benefits, the development, design, and large-scale implementation of continuous manufacturing, like traditional manufacturing, still requires early cooperation of chemists, process engineers, and even plant engineers. This helps keep the development process on track, eliminates the need to make premature decisions for any investment in large-scale plants, and, most importantly, delivers products with consistent, predictable quality.

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.

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Dr. Poechlauer joined Thermo Fisher Scientific in 1990 and possesses more than thirty-five years of experience in biocatalysis and oxidation chemistry. He is an expert in the application of innovative technologies, such as process intensification and microreactor flow chemistry, to small molecule API process development. A frequent presenter at industry conferences, Dr. Poechlauer has authored forty-seven patent applications, sixty publications and several book chapters. He received his doctorate in Natural Sciences in organic chemistry & pharmaceutical chemistry from Innsbruck University in Austria.

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