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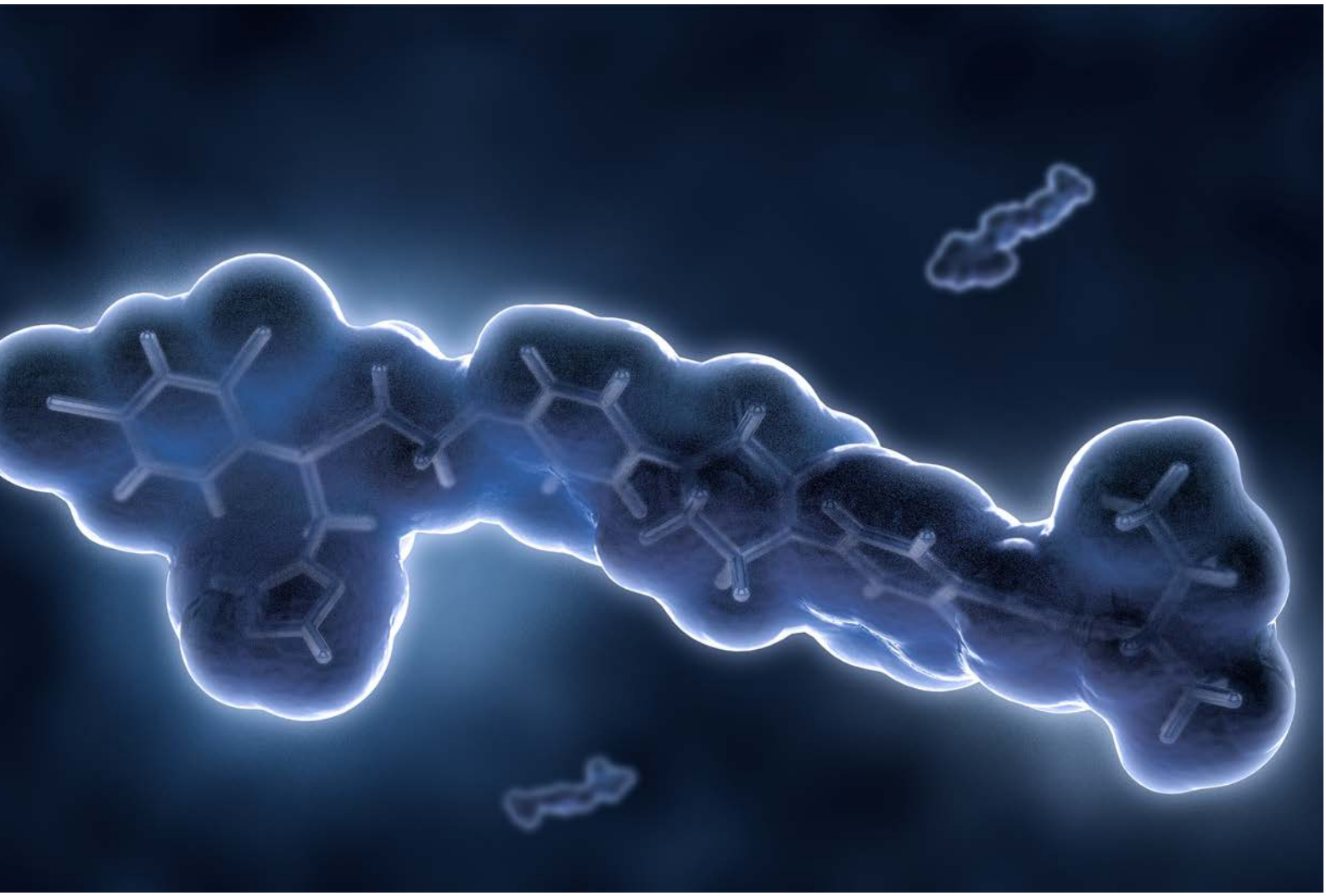

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WHITEPAPER

Flow chemistry: A scale-up solution for modern API development & manufacturing

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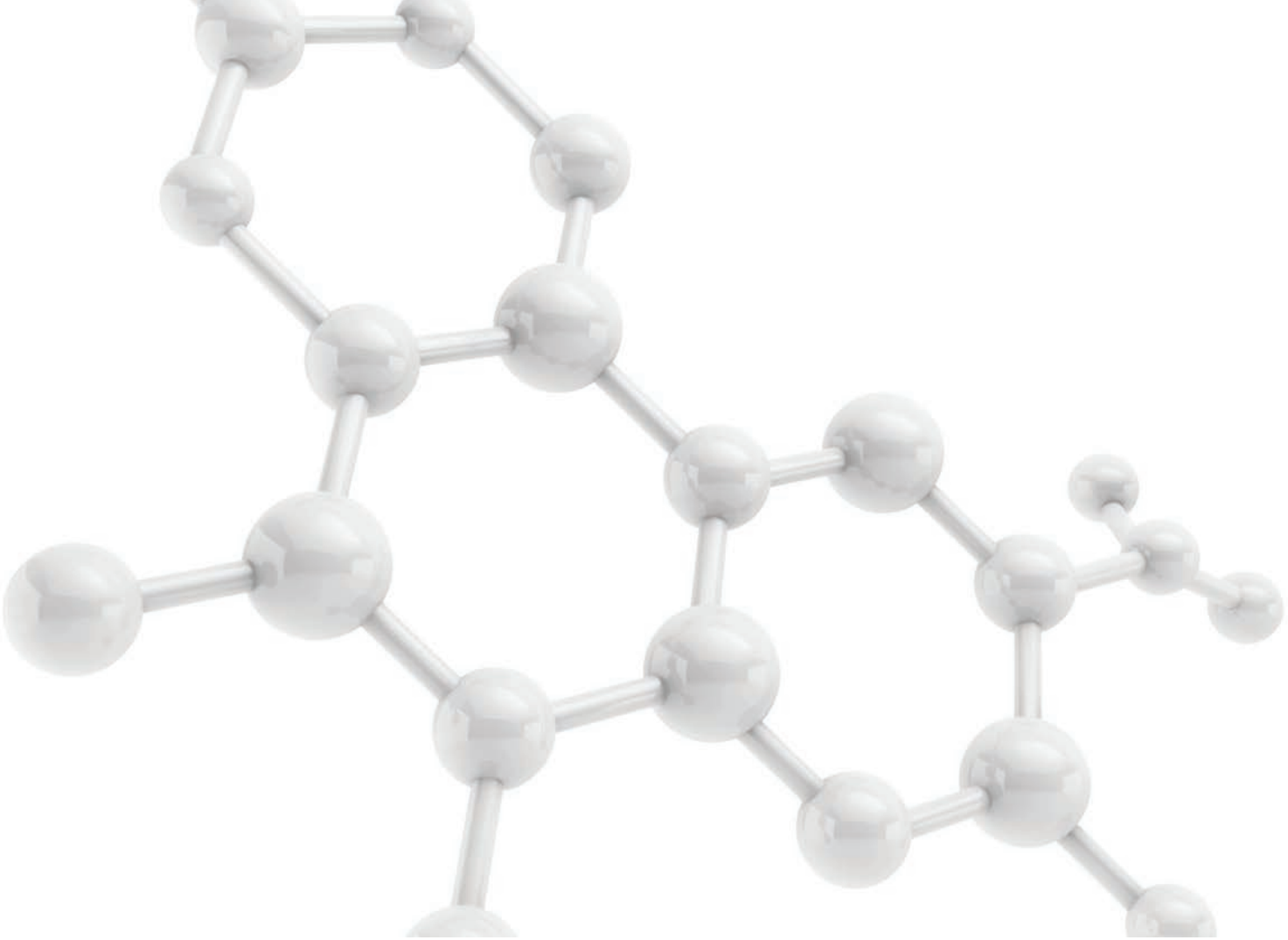


Abstract

Once deemed an “experts-only” approach to chemical synthesis, flow chemistry is a cost-efficient technique growing in popularity that can increase safety and flexibility and improve product quality. However, not all chemical profiles perform better under flow conditions. Thus, you must know how to evaluate whether your API will perform better with batch versus flow chemistry, as this dictates not only the process you will use for scale-up but also the facility and expertise needed to do it successfully.

Achieve better control and reproducibility with flow chemistry

Traditionally, pharmaceuticals are produced in batches, where reagents are added to the stirred tank and the desired product is formed using specified reaction conditions. If the volume demand increases, a chemist may need to optimize or even revise the synthesis so the API's quality attributes can be maintained at a larger scale. Process features—such as mixing times, reagent addition times, and reaction times—tested at a small scale will likely need to change at a commercial scale when equipment is larger and conditions differ. Should a company find out too late that the synthesis used for small-scale manufacturing is not scalable to larger production, it can have a devastating impact on its drug delivery timeline. For example, issues or mistakes that affect yield, product quality, or by-product profile may result in a failed batch, not only delaying material supply but also costing millions of dollars in lost product.

By operating continuously, the chemists can immediately see the effect on the product as it flows out of the reactor.

With flow chemistry, the starting materials, solvents, and reagents needed to form the product are sent through a flow reactor, where a heating/cooling jacket adjusts the temperature as needed while the reaction components are simultaneously added.

Chemists then determine the reaction parameters that affect product quality and yield and screen any interdependencies to identify what the parameters' ranges and interdependencies must be to deliver the product within the targeted specifications.

Once this is complete, they know how to modify the throughput of the plant and still maintain all parameters within those ranges. Thus, they can easily scale the process to the desired product volume.

By operating continuously, the chemists can immediately see the effect on the product as it flows out of the reactor. They can even accelerate the creation of process knowledge by speeding up the reaction data to learn how a reaction behaves as parameters are changed. Thus, a greater number of experiments can be performed in sequence to gain knowledge about reactions in a much more detailed and quicker way. In many cases, flow chemistry improves yield.

For example, in a batch plant, there are different positions in a stirred tank where the reagents experience completely different reaction conditions. Some starting material may encounter too much or too little of its reaction partner until it is mixed in, or some of the reaction areas might be hotter or colder than others. Varying reaction conditions at different positions of the reactor will lead to by-product formation. Every by-product that forms subtracts from the product yield. Because a flow process can be used to precisely tune the reaction conditions to be the same for every volume element of reacting liquids, a company can increase product yield and decrease by-products, leading to additional savings in purification efforts and raw materials. As a result, flow chemistry can consistently deliver product quality from small volumes to large volumes over the various phases of clinical development.

Scaling up: Batch versus flow

When scaling up a batch process, campaign time is, for example, multiplied by two by making 20 batches instead of 10. This is dependent, though, on other products and whether it is possible to free up a stirred tank of suitable size. Another option is to change the plant to one with larger stirred tanks, although this comes with some unknowns, such as what the temperature will be or how the mixing will perform in new reactors. Yet, with flow chemistry, a chemist can simultaneously develop a process and a plant by identifying what the reaction needs to produce a select product and then defining the required capabilities of the plant. Typically, flow plants have reaction volumes of liters, while a batch plant with an equivalent productivity will have cubic meters, resulting in a plant design that ends up being a fraction of the size of a traditional one.

If and when scale-up is needed, there are two options in a flow plant: either operate the flow setup at a prolonged time or multiply the flow setup by putting identical flow processes next to each other in the plant. This effort in a flow plant is limited compared to a traditional plant, where adding equipment would mean having to make room for large stirred tanks. However, scaling up a flow chemistry does require the appropriate technologies, equipment, and skillset. It also requires competencies beyond chemistry, such as continuous analytics, process technology, modeling skills, and flow plant engineering.

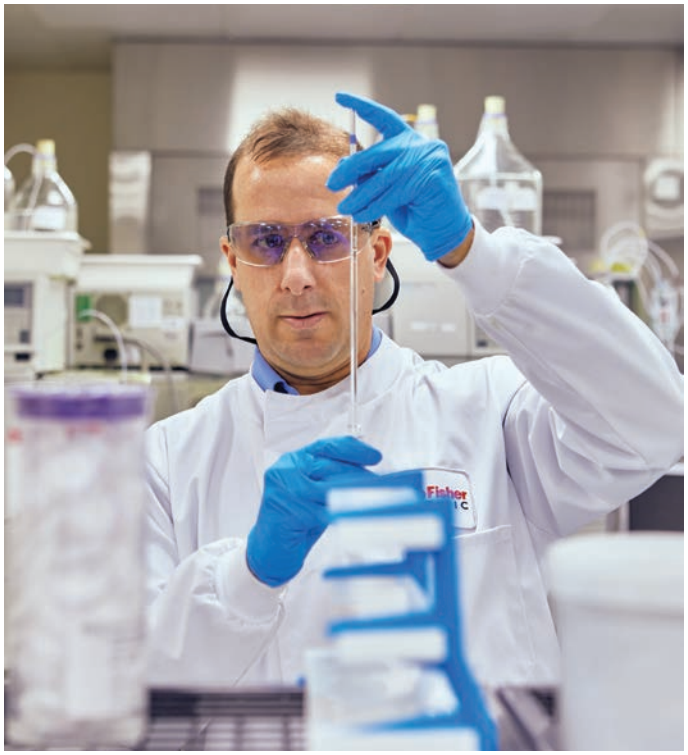
Flow chemistry facilitates scale-up, but is it right for your API?

Although flow chemistry can be used to scale up many chemistries, it is not a fit for all profiles. Using flow chemistry requires a wide range of expertise to identify if a synthesis can transition from batch to flow and what, if any, adjustments need to be made to scale up consistently and safely. A company can apply flow chemistry on its own if it has the appropriate in-house expertise to determine it is the best approach for its synthesis and the capabilities to execute it.

If it cannot, and scale-up requires the help of an outsourcing partner, the CDMO selected will analyze the chemistries the company has used and the properties of the starting materials and respective reactions to determine if a synthesis can transition to flow. For instance, are these slow reactions with harmless starting materials or reagents? Or are they fast, exothermic reactions?

Flow chemistry can be especially useful when using hazardous/unstable reagents in chemical synthesis routes. Conventional API manufacturing equipment does not provide the required mixing rates and heat removal capacity to safely use these reagents at a large scale.

Conversely, because flow reactors are much smaller, they allow for more precise temperature control and monitoring and, consequently, better containment of highly potent reagents, intermediates, and APIs. The smaller footprint with higher process intensity means a flow plant is not only faster, but it also uses less solvent, making it more economical. This, combined with its ability to produce more volume in a shorter amount of time, can cut capital costs and production time.



Case study: Transitioning a chemistry from batch to flow

Thermo Fisher Scientific recently worked with a client that had a metal-organic reaction with very hazardous reagents. The synthesis had been developed to work at minus 100 degrees Celsius. At higher temperatures, the chemistry began to form by-products and become unselective. Maintaining the necessary temperature would have required a cooling capacity, which is very costly. The team at Thermo Fisher determined flow chemistry would be a more appropriate means for scale-up of this reaction.

They began the transition with standard lab equipment, but to take it to the pilot plant, a flow reactor had to be built that would apply the exact same processing history to the starting materials identified in the lab. This required the chemists to work with their engineers to pinpoint the exact tubing with the length and diameter needed to construct the reactor. While a modular reactor can be used, it must be configured to meet the needs of the reaction, so not just any flow reactor could be used. After transitioning it from a batch reaction to flow, Thermo Fisher's experts were able to achieve the same selectivity and, even better, yield at only minus 70 degrees Celsius. The process was then able to run successfully from lab-scale to pilot plant to a full-scale plant, and the FDA has since granted approval of the API.

A future in flow

The FDA has encouraged the pharmaceutical industry to apply continuous manufacturing to keep up with the evolution of new pharmaceutical concepts and provide the growing number of new APIs at high quality and acceptable costs. This emerging technology can facilitate scale-up, improve product quality, and even address some of pharma's biggest challenges, such as drug shortages and recalls. Furthermore, knowledge about flow chemistry and its continuous approach to creating new molecules has increased throughout the industry as experts recognize its ability to open up new possibilities in chemical transformations. This is critical when the unmet needs of today's patient population are calling for more complex chemistries to deliver new drug therapies. Notable pharmaceutical manufacturers have reported cases of applying flow chemistry to address scale-up issues that would otherwise require multiple, and likely costly, steps to resolve.

For example, a recent article about flow chemistry in drug manufacturing describes one such case: "Pfizer and Snapdragon reported the synthesis of a chiral β-amino alcohol through a novel propargylation reaction that utilizes flow to intercept an unstable allenyllithium intermediate. This process was used to provide intermediate scale supply (15 g/h). This novel approach leveraged the mixing and heat removal capabilities of flow to conduct a reaction that would have otherwise not been possible in batch."[1] Several other examples in the article outline various instances in which flow chemistry offered a number of benefits when facing unique challenges from drug discovery to manufacturing.

Nevertheless, the author stresses the importance of the appropriate capabilities as well as "the ability [of scientists] to learn and apply skills from multiple disciplines outside their own expertise." An API is capable of transitioning to flow only if the resources are available to overcome the challenges of this innovative approach to drug development and manufacturing. Securing these resources in-house or working with a CDMO to reap the benefits of flow chemistry allows you to take a step forward and may be the competitive edge you need to get ahead in this modern era of drug manufacturing.

References

1. Akadémiai Kiadó, Flow Chemistry, Continuous Processing, And Continuous Manufacturing: A Pharmaceutical Perspective—https://akademiai.com/doi/full/10.1556/1846.2017.00029

About us

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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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Published 08/21

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