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Advanced Synthesis

Article

# Streamlining early phase drug development with continuous flow technologies

## Leveraging continuous flow technologies to address the growing complexity and potency of small molecules.

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**The pharmaceutical industry is witnessing a shift as small molecule drugs become increasingly complex and ever more potent. Advances in medicinal chemistry are driving the development of more sophisticated compounds, often with highly targeted mechanisms of action. These innovations, while promising, are also pushing the boundaries of traditional drug development, particularly in the early phases, where the need for rapid iteration and flexibility is critical.**

At the same time, there is growing pressure to shorten development timelines and reduce costs, while maintaining high standards of quality and safety. These trends are making early-phase drug development more challenging, as existing processes can be too rigid and slow to keep pace with the demands of modern drug discovery.

Batch manufacturing, the traditional method used for early-phase production, can become a bottleneck in this evolving landscape. Designed for larger-scale, simpler compounds, batch processes are slow, requiring time-intensive setup, validation, and scale-up between production runs. This stop-start nature creates inefficiencies, making it difficult to meet the demands for speed and agility for some early development projects.

## Going with the flow

Increasingly, early-phase drug developers are looking to use continuous flow processes to avoid some of the limitations of batch processing. Continuous flow processing is a manufacturing method where chemical reactions occur in a continuous, steady stream rather than in separate batches. Reactants are continuously introduced into the system, and products are constantly removed, allowing the process to run uninterrupted for a period of time, with the amount of product made depending on how long it is left running. This approach contrasts with traditional batch processing, where reactions occur in discrete steps, and production is halted between batches.

An important advantage of a continuous flow system is that it gives better control over hazardous reactions by operating in smaller volumes, reducing risks. Improved heat and mass transfer allows for faster, more consistent reactions with higher product quality. Continuous flow is therefore preferable to batch processing for safety reasons when handling hazardous or reactive chemicals. Under any circumstances, the improved heat and mass transfer can give faster, more consistent reactions, leading to better product quality.

The ability to operate at higher pressures, which enhances gas solubility and reaction rates, makes these systems ideal for processes involving gaseous reactants. The use of continuous processes also supports cost and resource efficiency by eliminating downtime, while also minimising solvent and energy use. Additionally, continuous flow can be adapted to encompass complex, multistep syntheses, making it a valuable approach for modern pharmaceutical manufacturing.

This is not to say that one of these distinct methods is superior to the other; rather, each has its specific use cases. Batch production will remain appropriate if the objective of production is volume, particularly if the reaction is a slow one. When process intensification is paramount, continuous flow can have significant advantages.

## Mini-mono plant technology

At Lonza Advanced Synthesis, the continuous flow process is integrated into early phase development, allowing for optimisation of chemical processes from pre-clinical work all the way to Phase III. As part of its work with continuous flow, the company has successfully completed more than 50 customer projects and its scientists have contributed to more than 50 peer-reviewed articles.

One such publication describes the potential of 'mini-monoplant' technology, utilising continuous flow to create dedicated, intensified pharmaceutical processes from early lab-scale to commercial production.[1] The mini-monoplant is a small, dedicated production facility that focuses on making a single product. The 'mini' in the name refers to the intensification of the product, which is achieved via continuous processing, the use of advanced reactor technology and a small factory footprint. The 'mono' refers to the fact that the facility is dedicated to a single product, regardless of whether it operates in batch or flow, with high levels of automation, and real time release testing.

The focus on a single product enables quicker and cheaper production, allowing companies to respond rapidly to market demands. The aim of the mini-monoplant is to facilitate the processing of more complex, potent, lower-demand, and specialised drugs that require an accelerated timeline to reach the market, and where demand levels are uncertain.

**The paper cites three key advantages of mini-monoplant production:**

1. The ability to develop best-in-class processes at the lab scale, where novel synthesis routes will improve the safety, sustainability, and yield.

2. To accelerate development and time to market through a streamlined scale-up to factory-based production facilities. The lab-scale process becomes the production set-up, which may be developed further and, when required, scaled up using established geometrical scale-up methodologies.

3. An overall reduction in capital and operating expenditures when the mini-monoplant is ultimately built and dedicated to the continuous production of a single product. This increases productivity while reducing the factory footprint and avoiding the changeover steps that are required with production in a multipurpose plant.

Figure 1 (next page) shows the reactor setup build in a modular fashion. The reaction is first conducted in a microreactor (FlowPlate technology®) to cope with the heat and aged in a coli reactor to gain volume and residence time.

**Figure 1**
Examples of fundamental continuous reaction technologies.

## The importance of know-how

Lonza Advanced Synthesis has built its expertise in continuous flow manufacturing over a number of years. This experience allows key problems with flow processes to be resolved quickly, including plugging and long-term stability, without timelines being impacted. At Lonza Advanced Synthesis, a dedicated team is ready to work with clients on their continuous flow plans, and the company has four laboratories dedicated to this type of project. In terms of the equipment used, the team has ready access to various reactor technologies, including plate, shell and tube, coil, and electrochemical.

Beyond Lonza Advanced Synthesis' experience with continuous flow manufacturing, there are other elements of its service that can help clients to successfully navigate their early phase development, particularly when dealing with complex APIs.

One such service is Lonza's AI-enabled Route Scouting, which uses AI to help process chemists design the best synthetic routes. Computer-assisted synthesis planning tools leverage predictive and analytical cheminformatics to identify promising reactions and routes. AI-powered technologies underpin *in silico* retrosynthesis, supply chain analysis, and process R&D evaluations with the help of extensive datasets. This allows for the automated generation and comparison of multiple synthetic pathways, enhancing efficiency and decision-making in the development process.

The combination of all these tools in a complete package allows Lonza Advanced Synthesis to offer a way to manage risk and investments through the team's technical expertise, facility capabilities, and engineering solutions. The end result is a manufacturing process that fits with the evolving needs of drug developers to deliver consistent scale up with improved safety, sustainability, and yield.

## References

[1] Doyle BJ.; Petteri Elsner P.; Gutmann B.; et al. Mini-Monoplant Technology for Pharmaceutical Manufacturing *Organic Process Research & Development 2020* 24 (10), 2169-2182. DOI: 10.1021/acs.oprd.0c00207.

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