

Continuous Manufacturing in the Pharmaceutical Industry

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Apply the fundamental principles of continuous process design and process intensification to change the pharmaceutical manufacturing status quo.

Process intensification (PI) in the pharmaceutical manufacturing industry has been demonstrated in bioprocessing and small-molecule drug facilities through the implementation of continuous manufacturing (CM). Some of the major benefits of CM include faster speed to market, better process control, smaller factories and environmental footprints, more consistent product quality, modular manufacturing, and lower capital and operating costs (1–3).

Although the product design, chemistry, biology, drug delivery method, and efficacy of the drugs are defined by chemists, biologists, and medical experts, equipment and process design are the domain of chemical engineers. Chemical engineers have the skills and tools to design efficient and robust processes to overcome the technical and economic barriers to CM.

Because the technoeconomic criteria, products, steps, and scales vary between applications, each CM process design should be tailored to the specific application. CM processes can be fully end-to-end continuous, a hybrid of batch and continuous, or individual continuous operations retrofitted in a batch process (mostly for legacy processes). Selection of the approach is guided by an evaluation of the product, process, equipment, regulations, enterprise readiness, technology availability, market demand, and volume

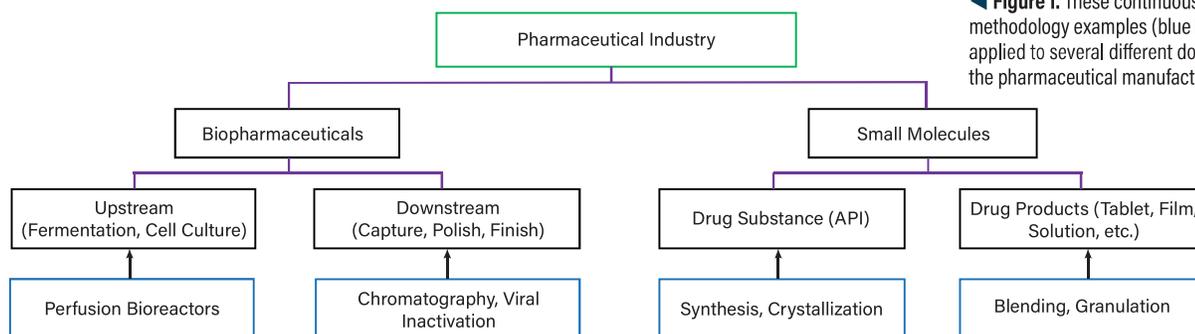
and/or value of the product.

Pharmaceutical manufacturing is a broad industry in which CM can be applied to different domains. Figure 1 indicates relevant CM methods that can be applied to discrete domains, but domains can be connected in an end-to-end fashion to create a fully continuous process. For instance, synthesis and purification (drug substance), formulation and blending (drug product), and tablet production can all be combined in one train (2).

Make more with less

From the PI point of view, CM can significantly reduce process footprints (spatial PI), production time (temporal PI), manufacturing costs, waste generation, and good manufacturing practices (GMP) management and costs. Table 1 demonstrates an example of the different types of savings in space, costs, and time that can be achieved in transitioning a tablet drug product process from batch to continuous.

Batch processes work in discrete time intervals that require startup, shutdown, cleaning, and validation time for each individual batch. Continuous processes have longer duration runs and multiple batches of materials can be manufactured continuously. CM can achieve the annual production rate of a batch facility in a much shorter time.



◀ **Figure 1.** These continuous processing methodology examples (blue boxes) can be applied to several different domains within the pharmaceutical manufacturing industry.

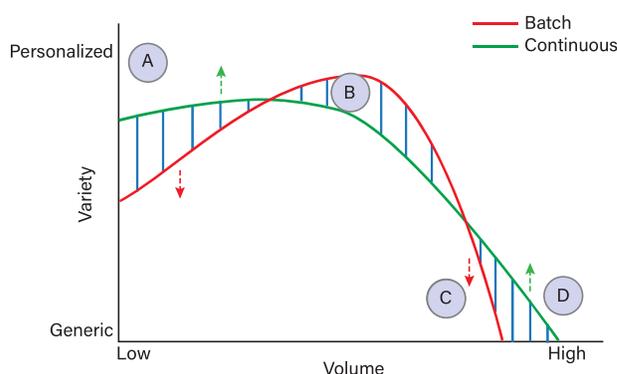
Table 1. Continuous manufacturing (CM) offers several benefits in this example of a facility that produces a tablet drug product.

Source	Batch	Continuous	Benefit of CM
Footprint	6 discrete unit operations, 7 rooms	1 equipment train, 2 rooms	Less energy, lower good manufacturing practices (GMP) facility cost
Manufacturing time	13 days	2 days	Lower cost, higher supply for demand response
Waste	3%	Around 1%	Sustainability, lower cost for goods
Testing	Off-line and release cycle (30 days)	In-line/At-line, cycle time less than 5 days	Faster and more data, lower cost for goods, supply chain advantages
Investment (CAPEX)	\$24 million	\$10 million	Lower cost for goods, faster depreciation
Supply flexibility	Regulatory filed batch in kg	Batch run time in 1–48 hr	Batch size can be adjusted to demand

The high-throughput nature of CM should be balanced with the market demand to maintain efficient asset utilization. The annual plant capacity (or market demand) should be the design basis to define either the time that a CM process at a specific scale should run to manufacture the required volume of product, or the size of the equipment (volumetric flowrate and residence time) to meet overall throughput and runtime requirements.

Such technoeconomic considerations make CM a viable option for certain market demands and various products, e.g., for high-volume generic products or low-volume personalized products (4). Figure 2 shows a high-level analysis of batch vs. continuous processing for different scenarios (1, 5). Point A represents a small-volume personalized product for which an intensified continuous process would be more viable. Point B is in a marginal area where medium production volume for an established product could be economical as either batch or continuous. Point C shows a case in which manufacturing a high volume of a generic product would be more profitable as a batch process. And, Point D is a generic product for which CM would handle the large production capacity at lower cost and higher profit margin.

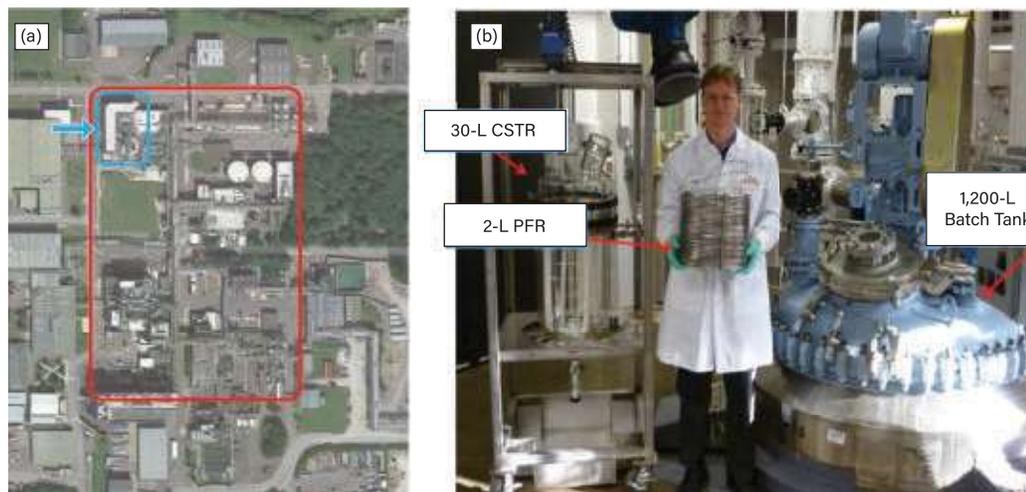
A combination of batch and continuous manufacturing would yield a hybrid process, where a particular step (such as crystallization) can be batch or fed-batch within a continuous plant, or a drug substance and drug product processes can be segregated in batch and continuous. For example, a GlaxoSmithKline (GSK) facility in Singapore produces fluticasone propionate continuously at high capacity. Then,



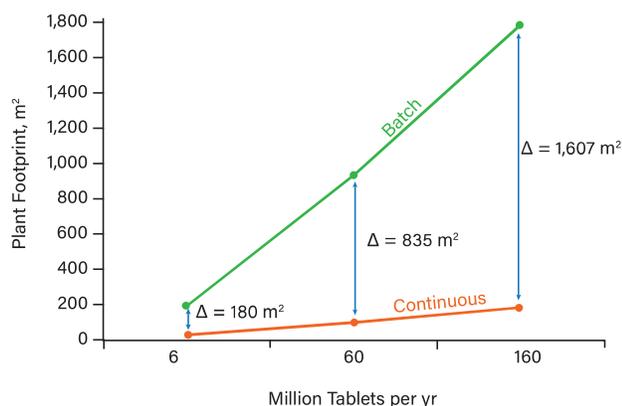
▲ **Figure 2.** Depending on the production volume and required level of personalization, batch or continuous processing may be more economical. Source: Adapted from (5).

the drug product is formulated via batch processing for a variety of product types (e.g., suspension nasal spray or dry powder inhaler) at different sites around the world from the same continuously manufactured active pharmaceutical ingredient (API) (6).

PI can help reduce the size and footprint of CM equipment while maintaining a constant overall annual production capacity. Auxiliary units such as heating/cooling capacity, pumps, and separators could also be intensified to improve their efficiencies and reduce footprints. The intention is to improve the CM facility's return on investment (ROI) by reducing the utility costs, waste management costs, and scheduling expenses.



◀ **Figure 3.** (a) At an Eli Lilly site in Ireland, the red box is the boundary of the old batch facility and the blue box is the new continuous facility. (b) A 30-L continuous stirred-tank reactor (CSTR) or a 2-L plug flow reactor (PFR) are capable of the same throughput as the 1,200-L batch reactor (7).



▲ **Figure 4.** For a batch process, large increases in tablet throughput necessitate large increases in plant footprint. The continuous process requires a much smaller increase in plant area (2).

Figure 3 shows Eli Lilly’s manufacturing site in Kinsale, Ireland, where a new CM line is being developed. The aerial view (Figure 3a) compares the old facility in the red box and the new CM facility in the blue box (7, 8). Although the footprint of the continuous process is much smaller, the annual manufacturing capacities of the batch and CM lines are almost equal. Figure 3b shows the equipment that has enabled this reduction in footprint and the traditional batch equipment. The 1,200-L batch reactor, 30-L continuous stirred-tank reactor (CSTR), and 2-L plug flow reactor (PFR) are all capable of producing the same amount of product in the same amount of time.

Increasing the throughput of a batch process requires a large increase in plant footprint. Figure 4 shows the plant area required for scale-up of a drug product (tablet). At 6 million tablets/yr, the difference between the batch and continuous plant’s footprints is 180 m²; at 160 million tablets/yr, this difference is 1,607 m².

In bioprocessing, perfusion bioreactors could provide

up to 10 times more viable cell density and volumetric production rate than batch or fed-batch reactors. The most critical advantage is that perfusion bioreactors are smaller in size and can produce the same product yield in less space. Traditional fed-batch bioreactor systems consist of tanks that are usually around 10,000–25,000 L. Cells are cultured in batches that typically run 7–21 days. In contrast, perfusion bioreactors culture cells over much longer periods, even months, by continuously feeding the cells with fresh media and removing spent media while keeping cells in culture.

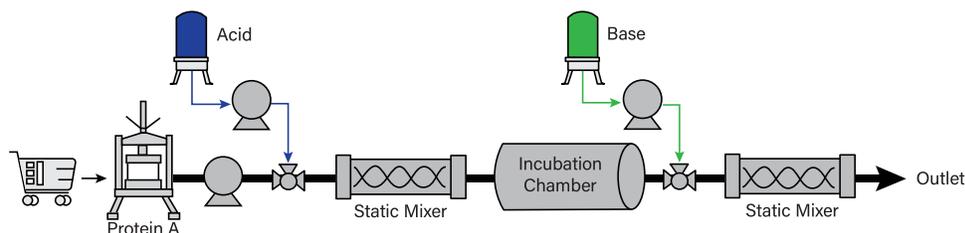
Unlike batch systems, perfusion systems do not accumulate waste products. Expressed proteins are rapidly removed and made available for purification. However, the continuous feeding of fresh media could increase the operating expenditures (OPEX) if the media is expensive. The techno-economic analysis should compare capital expenditures (CAPEX), OPEX, and throughput to define a point at which CM would become more economically viable.

Make more, better and faster

In addition to enhancing throughput and reducing plant footprint, CM can also improve product quality, e.g., by reducing impurities from side reactions, ensuring a narrow particle size distribution (PSD), and reducing protein damage in bioprocessing.

Impurity generation from side reactions in a synthesis step. Many unwanted side reactions can occur in a batch reactor. An intermediate could react with any of the starting materials or decompose during the long processing time. In a PFR, the concentration of starting materials decreases over time within a controlled volume and materials travel through the reactor at a fast rate, which hinders the progress of any side reactions and limit impurity formation.

In addition, the smaller scale enables better heat transfer, which prevents formation of localized hot zones and provides a more uniform temperature profile. If the reaction



◀ **Figure 5.** The Bio-Continuum virus inactivation platform by Millipore-Sigma mitigates many of the problems associated with traditional viral inactivation processes (9).

kinetics favor impurity formation at higher temperatures, a uniform temperature distribution in the reactor could reduce impurity formation, which would improve performance of the downstream purification steps and decrease impurity content in the final product.

Example 1. Continuous viral inactivation in bioprocessing. Most of the viral inactivation processes include addition of acid to a bioreactor product stream to deactivate any possible viruses. The batch process requires the addition of a large amount of acid to a large vessel, and the product must be held in the low-pH vessel for a long time to achieve the required deactivation. This low pH can damage the product by aggregating, unfolding, and denaturing its structure, as well as breaking and decomposing its proteins.

MilliporeSigma developed the continuous BioContinuum virus inactivation platform to address the problems with traditional batch viral inactivation (Figure 5) (9). A small amount of acid is added to a small volume of product and flows through a static mixer with a short residence time, which provides effective inactivation without damaging the protein product as much. An unpublished study compared the batch and continuous systems; the batch inactivation process damaged approximately 7% of monoclonal antibodies (mAbs) and the continuous platform damaged less than 0.5%.

Example 2. Impurity inclusion in a crystalline product. Crystallization is used to isolate and purify products, as well as reject impurities. The tendency for impurities to become incorporated in the product crystal lattice depends on the thermodynamic and molecular structure similarities of the product and impurity, as well as the solvent system, which is conceptualized by the equilibrium distribution coefficient:

$$\text{Distribution Coefficient} = \frac{(C_{imp}/C_H)_{s,final}}{(C_{imp}/C_H)_{sol,0}} \quad (1)$$

where C_{imp} is the concentration of impurity, C_H is the concentration of the host molecule, s is the solid phase, sol is solution phase, 0 is the initial point, and $final$ is the end point or product.

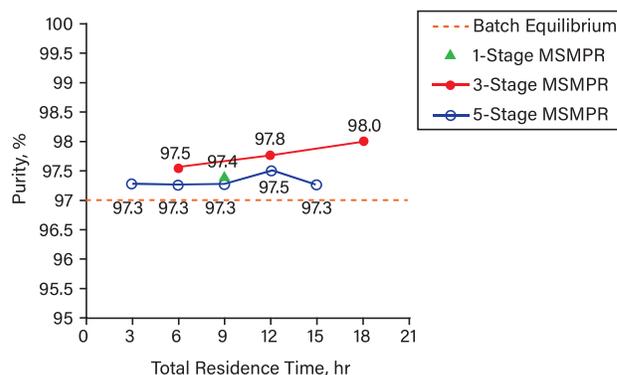
The actual impurity inclusion also depends on kinetics and growth rate, which is represented by the effective distribution coefficient (10). The distribution coefficient is a function of the concentration of impurity in the mother liquor phase — *i.e.*, higher impurity concentration in the solution will generate less pure crystals.

In a batch system, the concentration of impurity in the mother liquor increases during the processing time, which causes more impurity to be incorporated into the crystal lattice. However, in continuous crystallization, the continuous addition of fresh solution to the crystallizer keeps the cumulated impurity concentration consistently low, resulting in higher purity of the harvested crystals.

Figure 6 shows the purities of cyclosporine crystals that continuous systems can achieve relative to a batch process (11). The mixed-suspension, mixed-product removal (MSMPR) process achieves a higher overall purity than the batch process, however, the single-stage MSMPR process produces a lower yield (not shown in Figure 6). The multi-stage MSMPR schemes use different temperature profiles (supersaturation) to produce a higher yield at higher purities than the batch process. Three-stage MSMPR is shown to produce the highest purity in Figure 6.

Continuous systems like the multistage MSMPR provide the opportunity to take advantage of different crystallization driving forces, for instance, cooling crystallization to a certain yield in early stages and antisolvent crystallization at a later stage (12).

Example 3. Enabling technology for distributed manufacturing. Batch systems are never in equilibrium, as concentrations constantly change (*e.g.*, as the reaction progresses). In contrast, continuous systems are always at equilibrium, except during start up and shut down. Steady operation makes continuous processes easier to control. Once a CM process is stabilized at defined process condi-



▲ **Figure 6.** Continuous processes yielded higher cyclosporine purity than the batch crystallization process (11).

tions, there is no need to actively change temperature or flowrates based on a batch recipe. This equilibrium state and process steadiness provides consistent product quality, reduces lot-to-lot variation, and reduces waste or rejection of off-specification materials. In addition, implementation of process analytical technology (PAT) can allow continuous monitoring of key process parameters and product attributes.

CM is compatible with modular and agile distributed manufacturing platforms. The intensified process can be designed in a modular skid that can be deployed to the point-of-care location for on-demand manufacturing of medicines. The Massachusetts Institute of Technology (MIT) Pharmacy On-Demand project (now On Demand Pharmaceuticals, Inc.), funded by the Defense Advanced Research Projects Agency (DARPA), demonstrated a modular technology that can create a variety of products in multiple dosage forms at a capacity of thousands of doses per day (4, 13). Figure 7 shows a modular plant, which includes a synthesis section (right) on the back of the unit, a purification/isolation unit (left) on the front of the unit, and drug product section inside the cabinet below the isolation unit.

Chemical engineering workflow for CM process development

The fundamentals of continuous processes, such as residence time and residence-time distribution (RTD), dispersion, heat and mass transfer rates, mixing time, Damköhler number, and so on, are taught in core chemical engineering courses (14). When considering CM for a pharmaceutical application, the complexity of the processes and products, required quality consistency, and regulatory criteria add additional challenges. These complexities necessitate teamwork and collaboration between chemists, engineers (process, mechanical, automation), management, and regulatory teams. The diversity of constraints, requirements,



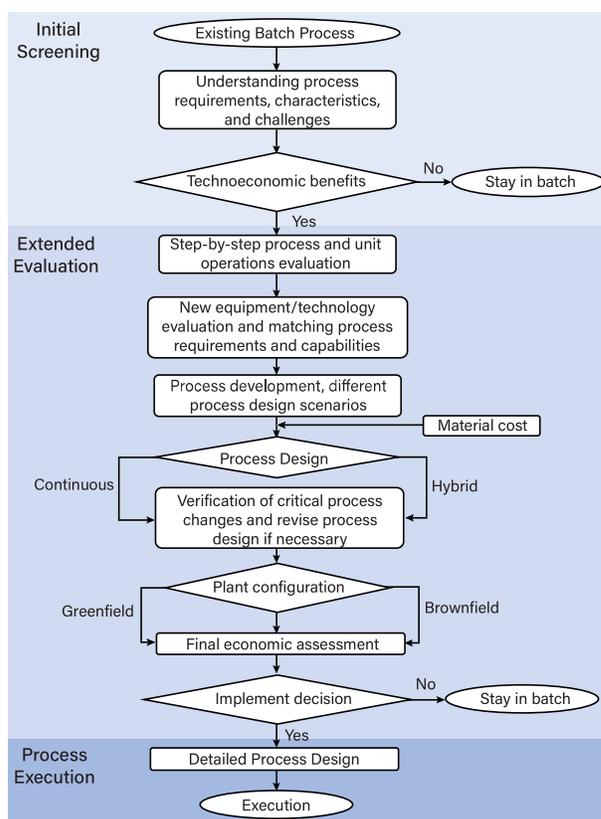
▲ **Figure 7.** This modular plant can manufacture a variety of pharmaceutical products on-demand (4).

organizational cultures, and technical languages can make CM process development a challenge.

Teoh *et al.* (15) proposed a decision-making methodology to evaluate converting pharmaceutical processes from batch to continuous or hybrid (16). It consists of three stages: initial screening, extended evaluation, and process execution (Figure 8).

Figure 9 summarizes the information required to execute this workflow for an example small molecule drug substance. The workflow begins by collecting the information about the molecule and synthesis route. This includes the main product, side products, reagents, and catalysts, as well as required reaction, purification, and crystallization steps. The medicinal chemistry team will provide most of the information for chemical engineers at this stage.

For most common pharmaceutical compounds, the chemistry is a multistep process of gradually making intermediates and possibly isolating certain intermediates between stages. The reactions can be multiphase and/or homogeneous and at different temperatures or pressures. Small-scale lab experiments at different residence times, temperatures, and concentrations produce estimates of kinetic parameters. Similarly, for purification, vapor-liquid-liquid equilibrium (VLLE) data is required for distillation,



▲ **Figure 8.** Teoh *et al.* proposed a methodology to convert pharmaceutical processes from batch to continuous or hybrid. Source: Adapted from (15).



or nucleation/crystallization kinetics for crystallization. In addition, heat-transfer rates, RTD, side reaction rates and mechanisms, yield, controllability, safety, and other classic chemical engineering design considerations are all required for process development (5).

Most of the processes, *e.g.*, heat transfer, mass transfer, crystal growth, mixing, etc., are scale-dependent. The scale-up study — from small lab scale to pilot and manufacturing — requires its own effort, and typically involves modeling and simulation (14). Although CM uses much smaller volumes than batch processes, even scaling up from microfluidics to a 10-mm inner diameter PFR is significant and requires a thorough study.

Crystallization is a challenging step for process development and scale-up. Many factors can cause lab-scale (*e.g.*, 50 mL) product quality or equipment performance to deviate at larger scales (*e.g.*, 10 L). Nucleation and crystal growth (and breakage/agglomeration or polymorph change) at a larger scale depend on mixing and heat and mass transfer. Cooling crystallization processes are prone to encrustation at the heat transfer surface. In contrast to MSMPRs, plug-flow crystallizers are capable of sequential multizonal heating/cooling to dissolve encrusts and to tune particle size (10).

Continuous anti-solvent and reactive crystallizations are more sensitive to mixing. For cases where the mixing underperforms, a low ratio of mixing to reaction/crystallization can push the PSD to an undesired range. However, the mixing performance is not easy to predict and control by simply increasing the speed. The high tip speed of the impeller could increase particle-particle, particle-wall, or particle-impeller interactions that could cause breakage, agglomeration, or generation of new fine seeds and heterogeneous nucleation (10). To avoid this issue, process designers perform computational fluid dynamics (CFD) parametric case studies with a variety of different impeller types, baffles (sizes, number, and location), and vessel designs and geometries.

Process integration and steady-state simulation

After individual equipment has been sized and characterized for the continuous process, engineers should perform flowsheet modeling at steady-state to map the process. At this stage, models can be used to perform sensitivity analy-

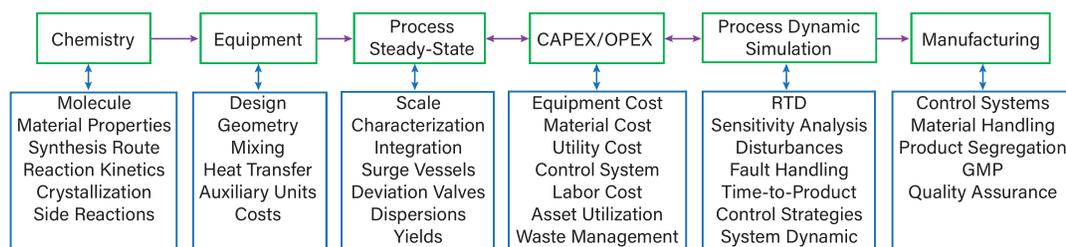
ses, define deviation valves placement, size surge vessels, balance the upstream and downstream flow, etc. Conventional simulation platforms (*e.g.*, Aspen Plus, gPROMS) are useful tools for this purpose.

A small nominal design margin should be added to slightly over-design the equipment and process for safety and process robustness in case of disturbances. For example, if a PFR reactor can provide a required conversion at a length of 1 m, the reactor would be designed to be 10–15% longer. That way, if a temperature disturbance occurs at the reactor heat source, or an inlet flowrate fluctuates, the reactor has extra capacity to deliver the required conversion. However, if side reactions lead to impurity formation, extra length/residence time can increase the outlet impurity to the point that the product goes out of specification. In this case, the design margin should be tighter to meet the purification capacity threshold.

Because the impurity concentration in the final product is highly important, an impurity fate-map should be developed from the steady-state models. The impurity fate-map tracks the concentration of important compounds in the process, including unreacted reagents, products and intermediates, impurities generated at each stage, impurities entering the process with inlet materials, catalysts, solvents, and any other components that would be treated as critical impurities in the final product. The impurity fate-map is one of the most important documents for quality control, quality by design (QbD), and regulatory communications. The accuracy of the model results and stream compositions should be validated by analytical chemistry testing, such as high-performance liquid chromatography (HPLC).

Steady-state models can also allow engineers to conduct a risk analysis and failure mode study. For instance, if some of the reactions produce insoluble intermediates or products with a tendency to precipitate out of the reaction, this could cause clogging of the pipes and equipment. In this case, the design engineer has two options:

- change the process/equipment (*e.g.*, use a CSTR instead of a PFR) or divide the challenging step into two steps to quench and restabilize the solution with additional solvent or at a different temperature
- add a significant amount of excess solvent to the step (and scale-up the equipment to the corresponding new volu-



◀ **Figure 9.** This diagram shows the workflow and flow of information and activities per step to develop a small molecule drug substance process using continuous manufacturing (CM).

metric flowrate) to solubilize the compound.

For the latter, more common option, the effect of increasing the size of the equipment and impacts to downstream equipment need to be further evaluated using simulations.

Defining and maintaining process parameters

Steady-state models can also be used for design space definition, which shows the correlation of process performance to process parameters.

A critical quality attribute (CQA) is a physical, chemical, or biological property that should be within an appropriate limit or range to ensure the desired product quality. A CQA may be defined by the product's bioavailability or toxicology, or downstream process requirements (e.g., particle size or flowability).

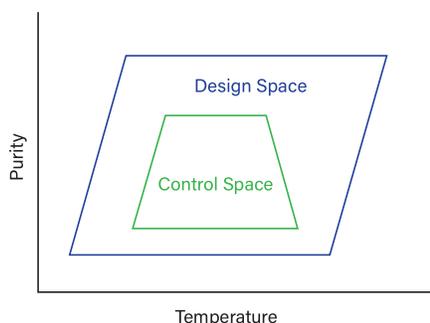
A critical process parameter (CPP) is an important process parameter that would contribute to variation in CQA, for example, reactor temperature that could increase impurity generation.

A critical material attribute (CMA) is a property of a raw material that could impact the process performance, e.g., an excipient powder's flowability in a drug product line that could cause component segregation in the final product.

Correlating CMAs to CPPs to CQAs by steady-state and dynamic modeling is a crucial step for defining process robustness and control strategies. The CQAs are mostly fixed constraints in the system. However, CMAs (e.g., different lots of raw materials from vendors) and CPPs (e.g., process disturbances, faulty auxiliary units) can vary along the process.

QbD is a systematic approach to process and product development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. QbD knowledge development involves determining how to maintain the CQAs by changing CPPs or applying control strategies to deliver constant quality products.

Risk assessments are used to prioritize process parameters and material attributes for experimental verification. After experiments are conducted, prior knowledge and



◀ **Figure 10.** Prior knowledge, experiments, and process performance help establish a design space. A control strategy within the design space can be developed using a quality-by-design (QbD) approach.

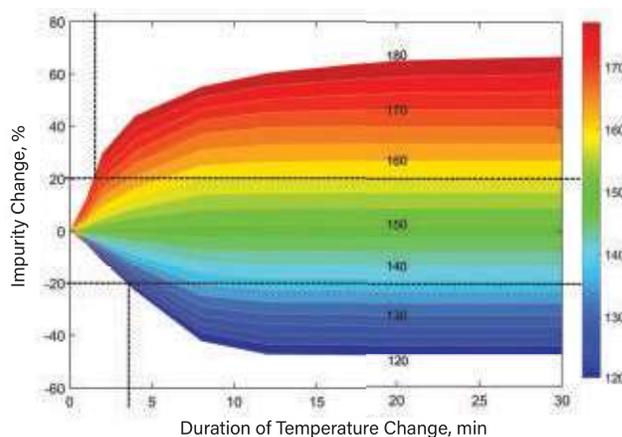
experimental data are combined to establish a design space. A control strategy for the entire process is established that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment. For example, if the temperature of the reactor impacts the quality of the final product, QbD will help determine how small the control space should be within the design space (Figure 10).

Dynamic simulation

Dynamic simulations are performed in the later stages of process development. These simulations evaluate system dynamics, taking into account possible disturbances, dispersions, and RTDs for individual unit operations and the entire line. Understanding process dynamics as a function of input material attributes, process conditions, or equipment design elements enables material traceability during and after production. This knowledge is essential for identification and mitigation of risks to product quality.

A single RTD analysis is not adequate for this analysis of system dynamics. Instead, a series of magnitudes and durations of disturbances should be analyzed. The RTD models for each magnitude and duration should be convoluted in the system RTD and used to develop funnel plots. These funnel plots show the system robustness, enabling evaluation of the tolerability of magnitudes or durations of disturbances.

Figure 11 is an example of a funnel plot for a drug substance CM line where the impact of reactor temperature disturbances were evaluated based on the final impurity of the products (17). The dashed lines in the plot show the safe region (state of control) for disturbances. Here, one minute of 30°C increase of reactor temperature is tolerable, but three minutes of 30°C increase of reactor temperature would create



▲ **Figure 11.** Funnel plots represent the system dynamic for a series of disturbances and RTDs. This plot shows the impact of temperature disturbances on the final impurity of the products (17).



an unacceptable condition. In a period when nonconforming material is produced, the amount of diverted material will depend on the duration and severity of the disturbance, system process dynamics, and location of the diversion point.

The dynamic simulation should focus on the process at a state of control (not the start-up and shut-down time) and evaluate disturbance scenarios during the steady manufacturing time. Dynamic modeling outcomes include risk analysis, control strategies, mitigation plans, alarm setpoints, and volume and location of surge vessels and deviation valves (17).

PAT is one of the main components of a CM line. Batch systems mainly rely on offline tests and analytical chemistry for quality control. In CM processes, on-line or in-line PAT tools are synced with the supervisory control and data acquisition (SCADA) system to monitor the process performance and alert the operator of any deviation from the state of control (18). Active control tools maintain process control and allow continuous release of product downstream, or, by a real-time release testing (RTRT) paradigm, allow the release of the final product to collection vessels.

The process understanding and fundamental knowledge of transport phenomena encapsulated in QbD, in combination with PAT, enable application of advanced process control (e.g., feedforward, model predictive control) to proactively control the CM process and equipment. While advanced process control has been demonstrated in some applications, it is currently not common in CM, mostly due to regulatory criteria.

Closing thoughts

The benefits of pharmaceutical manufacturing PI via CM are apparent. However, economic and regulatory challenges have delayed the transition from batch to continuous. Development of innovative equipment, modeling and simulation tools, digital platforms, and advanced process control technology could expedite this paradigm shift. Chemical engineers will have a crucial role in advancing CM and can apply lessons learned from other sectors, such as the petrochemical industry.

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