Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance

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ABSTRACT: This whitepaper highlights current challenges and opportunities associated with continuous synthesis, workup, and crystallization of active pharmaceutical ingredients (drug substances). We describe the technologies and requirements at each stage and emphasize the different considerations for developing continuous processes compared with batch. In addition to the specific sequence of operations required to deliver the necessary chemical and physical transformations for continuous drug substance manufacture, consideration is also given to how adoption of continuous technologies may impact different manufacturing stages in development from discovery, process development, through scale-up and into full scale production. The impact of continuous manufacture on drug substance quality and the associated challenges for control and for process safety are also emphasized. In addition to the technology and operational considerations necessary for the adoption of continuous manufacturing (CM), this whitepaper also addresses the cultural, as well as skills and training, challenges that will need to be met by support from organizations in order to accommodate the new work flows. Specific action items for industry leaders are:

- Develop flow chemistry toolboxes, exploiting the advantages of flow processing and including highly selective chemistries that allow use of simple and effective continuous workup technologies. Availability of modular or plug and play type equipment especially for workup to assist in straightforward deployment in the laboratory. As with learning from other industries, standardization is highly desirable and will require cooperation across industry and academia to develop and implement.
- Implement and exploit process analytical technologies (PAT) for real-time dynamic control of continuous processes. Develop modeling and simulation techniques to support continuous process development and control. Progress is required in multiphase systems such as crystallization.
- Involve all parts of the organization from discovery, research and development, and manufacturing in the implementation of CM.
- Engage with academia to develop the training provision to support the skills base for CM, particularly in flow chemistry, physical chemistry, and chemical engineering skills at the chemistry–process interface.
- Promote and encourage publication and dissemination of examples of CM across the sector to demonstrate capability, engage with regulatory comment, and establish benchmarks for performance and highlight challenges.
- Develop the economic case for CM of drug substance. This will involve various stakeholders at project and business level, however establishing the critical economic drivers is critical to driving the transformation in manufacturing.

Keywords: drug substance; continuous manufacturing; synthetic methods; crystallization; PAT; quality; safety; skills

INTRODUCTION—THE FUTURE FOR CONTINUOUS DRUG SUBSTANCE MANUFACTURE

Successful innovation in manufacturing and the adoption of continuous manufacturing (CM) has an important role to play in the industry's future. The vision for CM in the pharmaceutical industry is to exploit continuous processes to convert raw materials into safe, effective, and high-quality medicinal products. This vision is driven by the potential to improve control over quality, reduce costs, enhance process safety, and significantly reduce the timelines currently involved across the medicines' supply chain. In the shorter term, continuous processes in Good Manufacturing Practice (GMP) manufacturing will likely be single steps or reactions in series with batch workup and isolation, rather than the longer term vision of fully continuous end-to-end processing. As new continuous systems and technologies become fully established so the industry's

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ability to continue to meet the demands for existing as well as new, safer, and increasingly personalized dosage forms will be enhanced.

This whitepaper is focused on the opportunities and challenges associated with the first stages of this emergent pharmaceutical manufacturing paradigm, specifically continuous synthesis, workup, and isolation of new chemical entities, active pharmaceutical ingredients (APIs), or drug substances. In particular, the challenges and opportunities associated with each of these operations are highlighted alongside other important considerations when deploying continuous processes. Ensuring quality and consistency through control are key drivers for CM, and considerations for delivering the required levels of quality at each stage are discussed, highlighting some of the important differences from traditional batch manufacturing approaches. Flow chemistry is often cited as having advantages for safety in enabling access to hazardous chemistries in a safe and controlled manner.[1–5] However, a broader range of issues needs to be addressed to ensure safe operation at all stages. CM also changes the development paradigm (e.g., how and when process development is carried out) and the facilities strategy (e.g., current footprint versus future) and places markedly different demands on organizations and their staff compared with batch. Successful deployment of CM is therefore dependent on changes in organizational culture and workforce skills as well as in the science and technology. This whitepaper draws on the experience and informed views of many individuals from the industrial and academic community and recognizes that delivering this advanced manufacturing vision will require significant change across the industry and the wider pharmaceutical value chain.

REACTIONS: THE WIDER ADOPTION OF CONTINUOUS FLOW STRATEGIES IN PHARMA

Continuous flow synthesis has matured as a scientific area translating from a principle domain of chemical engineering to a technological tool now routinely used by many chemical synthesis laboratories and increasingly in process development and scale-up.[1–5] Conducting synthetic reactions in flow can be used to access a variety of benefits that may include: (1) reduced hazard/increased safety from smaller reactor volume, relative ease of containment, reduction/removal of headspace, reproducible delivery of conditions to ensure consistent quality with no accumulation of reactive/toxic intermediates; (2) reduced cost from lower capital and operating costs as well as improved consistency; (3) enhanced mass and heat transfer rates; (4) improved yield through enhanced selectivity; (5) expansion of the feasible reaction space offering a toolbox that can support many "forbidden reactions" through access to highly selective chemistries that would be difficult or impossible using batch, particularly at manufacturing scale; (6) ability to operate cryogenic processes at higher temperature; (7) safe, controlled access to higher pressure and temperature operation to enable operation at conditions that maximize yield and minimize impurity formation; (8) increased robustness, control, and stability inherent in steady-state operation of continuous processes; (9) easier, well-defined scale-up routes for laboratory to production scales; (10) increased throughput with a dramatically reduced equipment footprint; and (11) greener operation from reduced solvent consumption. Clearly, the actual benefits will be process specific; however, methods for assessing these and informing the early decision processes are required.

Widespread adoption of flow processes in pharmaceutical manufacturing facilities has not yet taken place. Until recently, this processing approach was almost exclusively confined to petrochemical and bulk chemical manufacturing settings. Perceived barriers in Pharma application include high skills and technology requirements combined with a limited ability to support multiple products because of product specific requirements of CM plant. Plant economics ultimately determined that such units were mostly commercially viable for very large-scale production generating large volumes of relatively simple compounds. The challenge for adoption of continuous flow manufacturing by the fine chemical sector has always been the diversity and complexity of the molecules of interest and the associated need for complex and diverse processing conditions. Typically, pharmaceutical and agrochemical molecules require 6–10 synthetic steps (sequential or convergent), involving chemo- and regio-selective transformations, that also necessitate multiple rounds of quenching, workup, separation, and purification. This is an important reason why batch processing dominates in pharmaceutical and agrochemical production as a small number of temperature- and/or pressure-controlled, agitated vessels can be used for virtually all of the reactions, liquid–liquid extractions, distillation, stripping, adsorption, and crystallization unit operations associated with a long and complicated synthetic route. The creation of integrated, self-supplying continuous processing streams is challenging. Although reaction kinetics can be manipulated using temperature, pressure, or solvent choice, for example, robust integration requires the controlled and steady balancing of reaction rates and process flows of sequential steps in addition to consideration of subsequent downstream operations. Adding buffering capacity between groups of synthetic steps is one option to help mitigate integration issues.[6]

One of the main impedances to the wider adoption of flow processing has been the delivery of readily tailored and amenable chemistry. Most routes conceived during small-scale laboratory development have historically been batch based and have therefore subsequently progressed through the various rounds of scale-up using related processing strategies. Only recently has an appreciable acknowledgement been made that potentially different development routes are required for continuous flow-based manufacturing sequences. This has resulted in a steady increase in the adoption of flow-based reactors at earlier stages of the development pipeline ensuring continuous processing is more readily built into the design and synthesis of new chemical entities. Automated flow-based techniques enable optimization and determination of chemical mechanisms and kinetics determined at the milligram scale.[7,8] Classical chemical reaction engineering concepts can then allow scaling of several orders of magnitude to production systems. Automated flow reactors are of particular interest as they offer rapid ways to quench reactions chemically or thermally and improve chemistry selectivity. Achieving improved selectivity is of considerable importance in integrated processes as it can lead to simplified workup stages downstream. Even so, continuous extraction, distillation, crystallization, filtration, and drying unit operations will be needed in some circumstances to achieve 99.9% purity APIs or in end-to-end continuous processes.

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