Control Systems Engineering in Continuous Pharmaceutical Manufacturing May 20–21, 2014 Continuous Symposium

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ABSTRACT: This white paper provides a perspective of the challenges, research needs, and future directions for control systems engineering in continuous pharmaceutical processing. The main motivation for writing this paper is to facilitate the development and deployment of control systems technologies so as to ensure quality of the drug product. Although the main focus is on small-molecule pharmaceutical products, most of the same statements apply to biological drug products. An introduction to continuous manufacturing and control systems is followed by a discussion of the current status and technical needs in process monitoring and control, systems integration, and risk analysis. Some key points are that: (1) the desired objective in continuous manufacturing should be the satisfaction of all critical quality attributes (CQAs), not for all variables to operate at steady-state values; (2) the design of start-up and shutdown procedures can significantly affect the economic operation of a continuous manufacturing process; (3) the traceability of material as it moves through the manufacturing facility is an important consideration that can at least in part be addressed using residence time distributions; and (4) the control systems technologies must assure quality in the presence of disturbances, dynamics, uncertainties, nonlinearities, and constraints. Direct measurement, first-principles and empirical model-based predictions, and design space approaches are described for ensuring that CQA specifications are met. Ways are discussed for universities, regulatory bodies, and industry to facilitate working around or through barriers to the development of control systems engineering technologies for continuous drug manufacturing. Industry and regulatory bodies should work with federal agencies to create federal funding mechanisms to attract faculty to this area. Universities should hire faculty interested in developing first-principles models and control systems technologies for drug manufacturing that are easily transportable to industry. Industry can facilitate the move to continuous manufacturing by working with universities on the conception of new continuous pharmaceutical manufacturing process unit operations that have the potential to make major improvements in product quality, controllability, or reduced capital and/or operating costs. Regulatory bodies should ensure that: (1) regulations and regulatory practices promote, and do not derail, the development and implementation of continuous manufacturing and control systems engineering approaches; (2) the individuals who approve specific regulatory filings are sufficiently trained to make good decisions regarding control systems approaches; (3) provide regulatory clarity and eliminate/reduce regulatory risks; (4) financially support the development of high-quality training materials for use of undergraduate students, graduate students, industrial employees, and regulatory staff; (5) enhance the training of their own technical staff by financially supporting joint research projects with universities in the development of continuous pharmaceutical manufacturing processes and the associated control systems engineering theory, numerical algorithms, and software; and (6) strongly encourage the federal agencies that support research to fund these research areas. J Pharm Sci
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INTRODUCTION TO CONTINUOUS MANUFACTURING AND CONTROL SYSTEMS

In recent years, pharmaceutical companies, federal agencies, and some universities have become interested in the development of technologies for the continuous manufacturing of drug products. In addition to benefits in terms of providing improved quality of drug product from translating existing batch processes directly to continuous, many examples have been published in which orders of magnitude improvements in process efficiency or controllability have been demonstrated. Many of the driving applications have involved the invention of very fast or high-pressure organic chemistry pathways that can only be effectively operated in small-scale continuous-flow reactors.[1–4] Very fast chemical reactions typically cannot be operated in a batch because of the poor spatial homogeneity in batch vessels and the inability to transfer heat at a rate that is high enough to avoid the generation of undesirable by-products or thermal degradation of the desired drug compound. Another set of driving applications that have been used to manufacture commercial drug products have applied continuous-flow mixers to produce drug crystals with very narrow size distributions (see Fig. 1), with a degree of size uniformity that cannot be achieved in a batch because of spatial inhomogeneity.[5]

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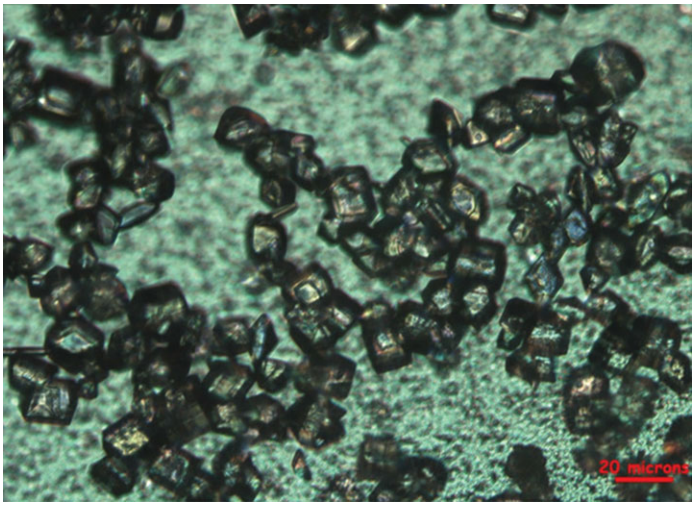

Figure 1. Crystals produced in continuous-flow by a dual-impinging jet mixer.

Continuous processes require control systems to ensure that the products are of high quality. Continuous pharmaceutical manufacturing processes can range from chemistries that involve only fluids, where substandard fluid can often be mixed with above-standard fluid to produce a fluid mixture that satisfies specifications, to solids whose specifications cannot be met in this manner. For the pharmaceutical industry, the control systems must provide a higher assurance of consistent product quality than what is required in most processes in the chemical, oil refining, and petrochemical industries. The objective of this paper is to provide a perspective of the current state of control systems engineering in the pharmaceutical industry and discusses the technical needs, challenges, and future research directions to facilitate the deployment of control systems technologies so as to ensure persistent quality of the drug product.

As an introduction, it is useful to provide a high-level description of the needs for control systems in the pharmaceutical industry. Very few manufacturing operators in the industry have any process automation or control expertise, so it is especially important that the control interfaces be user-friendly, while providing accurate and consistent control of the manufacturing facility and enabling the user to monitor and interface with the facility in a safe and efficient manner. The control system should provide only the necessary functionality, without having an overly complicated human–machine interface, to allow the operator to routinely verify that process parameters are within normal operating ranges and acceptance limits and that, when alerts and alarms are triggered, the necessary actions can be determined quickly, without scrolling through multiple views. System architectural design should not involve unnecessarily complicated and time-consuming development to customize the software to the particular plant, to allow for easy maintenance.

Other considerations required of the overall system are the maximization of the uptime versus downtime ratio, minimization of maintenance requirements, inclusion of performance diagnostics, and capability of future expansion. At first glance, these requirements may seem formidable, but much of the technical framework for such control systems already exists in other industries, such as oil refining, chemicals, and petrochemicals where such features are business as usual. As stated above, there are compelling differences, because of pharmaceutical products having a much higher requirement for continual assurance of product quality during processing than for nonpharmaceutical flow systems, but enough of the technical framework is in place that the control systems engineering can develop at a much faster pace for the continuous-flow manufacture of drug products than the fifty plus years it took for control systems engineering to develop in other industries.

The remainder of this paper begins with a discussion of the current needs for control systems engineering in the continuous manufacture of pharmaceutical products, and the technical barriers to addressing these needs. Then what industry, regulatory bodies, and universities can do to facilitate working around or through these barriers to develop control systems engineering technologies for continuous manufacturing is discussed. This discussion is followed by a description of existing and future control systems engineering technologies that could be of the most benefit to continuous pharmaceutical manufacturing, and a discussion of research directions that should be pursued to develop these technologies.

CURRENT STATUS AND NEEDS

Steady-State and Dynamics in Continuous Manufacturing

In the chemical engineering field, steady state refers to operations in which none of the variables in the system vary as a function of time. For a manufacturing facility, steady state refers to all process variables—including pressures, temperatures, compositions, tank levels, and flow rates—and all variables associated with the control system, such as setpoints, measured variables, and manipulated variables. Steady state is sometimes a useful idealization, but the term is much more commonly used by those who are not control engineers rather than by those who are. The reason for this difference in usage is that control engineers know that any real industrial system is never operating at steady state because of disturbances, such as pressure fluctuations, variations in the temperature of the surroundings that affect that rate of heat transfer to the system, and its variations in the compositions of the chemical feedstocks. Furthermore, many unit operations, such as adsorption, ion exchange, and chromatography columns cannot be operated under steady-state conditions and are typically operated at the industrial scale with multiple columns with time-varying flows that switch between the columns. Additionally, many variables have no incentive for being held at a constant value, with one common example being the level of a tank. The level of a tank is not a product quality specification, and so a common strategy used by process control systems is to actively vary a tank level to produce smaller time variations in a variable that directly impacts product quality.[6] It is also common for a drug product to have an allowed range of critical quality attributes (CQAs), with no clear benefit for being exactly at setpoint values. For example, the concentration of an impurity in the drug product typically has an upper boundary with no penalty for further reduction of the impurity. In this case, it is often possible to improve process efficiency or enable one set of CQAs to stay within its specifications by allowing another CQA to vary while staying within its acceptance limits.[7] Certainly, meeting all of the CQA specifications is more desirable than violating specifications because of a perceived desire to try to force all of the CQAs to be at some nominal "steady-state" values.

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