

# Achieving Continuous Manufacturing

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Clive Badman and Bernhardt L. Trout

## Continuous Manufacturing White Papers

The white papers presented here are a remarkable collection of work, unified by the goal of building upon the in-roads that continuous manufacturing has made in the pharmaceutical industry to turn it into the standard approach. Why this goal, and why now? The pharmaceutical industry is going through a period of great change as it goes over the Patent Cliff. Fewer blockbusters are being discovered, R&D productivity is down, and more molecules are aimed at niche markets. In the face of this, we have to ask, do we have the correct architecture for manufacturing in the industry? To date, we have largely been focused on blockbuster manufacturing with large, often separately located, drug substance and drug product facilities. Now is the time to look at new infrastructure with smaller, more agile facilities for end to end manufacture.

The industry has certainly been aware of these changes and the need to execute manufacturing differently. Over the past decade there have been significant investments in continuous manufacturing development, measuring well over a billion dollars in aggregate. These investments have, for the most part, been made by different companies pursuing internal projects with little communication or collaboration across the industry. The consequence is that, while there have been some benefits realized, the enormous potential of continuous manufacturing is not yet manifest, and the initial investments have not been recouped. We believe that the industry's uniting in an industry-wide focus on continuous manufacturing will add fuel to the flames of continuous manufacturing development. Janet Woodcock, Head of CDER at the FDA believes the same, and she asked us to organize a broader forum across the industry. These white papers, together with the symposium, are our way to help drive the industry towards reaping the true benefits of continuous.

Why are these white papers remarkable? They are remarkable for several reasons. First, they are a product of the industry as a whole, from companies of all types and sizes, consultants, regulators, and academics. Drafts were initially written by teams of professionals, who have spent their careers developing approaches to continuous manufacturing and advocating for it. These drafts were only a starting point. The white papers were posted on-line for public comment in April, 2014. Based on the feedback received, revisions were made, and the revised versions presented at a symposium at MIT May 20-21, 2014. Based on the discussions at the symposium, the papers were revised again and posted on-line for public comment in June of 2014 and final versions were sent to press in August, 2014.

Second, they are remarkable because, as an industry, we have been able to achieve some consensus on the key aspects of continuous manufacturing: what its potential is and ways to achieve it. Different people have varying ideas of how best to implement continuous manufacturing, and it is likely that the optimal approach for implementation will differ depending on the specifics of a given organization. Different people make different judgments about which are the most promising technologies. Different people have differing levels of immediacy depending on their current tasks. Still, we have a consensus on the big picture of continuous manufacturing, a consensus that should turn words into action for the benefit of the industry as a whole.

We do believe that these white papers, together with the Continuous Symposium, mark the end of a decade long era such that the old question of, “Should we do continuous manufacturing?” has shifted to, “How do we best implement continuous manufacturing?” The end of any era marks the beginning of a new one, in this case, the era of continuous manufacturing. Let us continue to answer this new question together!

## What is Continuous Manufacturing?

The vision of continuous manufacturing is of an industry with processes that are integrated, based on a systems approach, having model-based control, and making use of flow. Thus, seeing as a continuous manufacturing process is designed as a whole, the distinction between upstream and downstream or drug substance and drug product ultimately disappears. Given that continuous manufacturing encompasses integration, a systems approach, flow, and model-based control, future continuous facilities will be set up quite differently than existing facilities. There will be fewer partitions and few to no hallways, as equipment will be placed in larger areas where it can be engaged on-demand as needed for a particular process. Likely, any existing partitions will be chosen to separate different product safety classes so proper protective equipment would be used in a given location. Perhaps any necessary particulate handling would be done in separate partitions and the main production floor would consist of only equipment and piping with pharmaceutical materials never exposed to the atmosphere. Even cleaning could be performed without opening the equipment.

Because quality control would be performed inline, there would be no separate quality operations at the facility, although development work might be performed there. Processes will be run 24/7 for 50+ weeks a year with a week or two for annual maintenance. The facility will be modern, streamlined, with little presence of personnel on the floor, except for set-up, shut-down, troubleshooting, and maintenance.

Continuous manufacturing will lead to reduction of process steps, smaller footprint, smaller equipment, and higher product quality, all leading to cost savings, reduced risk of product failure and stock-outs, and in the end, better pharmaceuticals for patients. Integration within a systems approach itself leads to reduction of process steps, as the number of “correction” steps can be reduced or eliminated. The opportunity for the pharmaceutical industry to benefit truly from continuous manufacturing is now.

## The Future of Pharmaceutical Manufacturing is Now

Achieving the vision of continuous manufacturing will not happen immediately. To start we need to ensure that the necessary skills are sufficiently available. Furthermore, there is inertia in the industry that spans from large current capital investments in batch manufacturing to established approaches based on batch processing to get products out with a short timeline. All that this means, however, is that the industry should develop a workable approach for the transition. Since the future of the industry is continuous manufacturing, the time to start realizing the vision and thus reaping the full benefits is now.