2012 11 13 Symposium on Continuous Manufacturing of Pharmaceuticals Notes

These are notes from the first open meeting regarding Novartis-MIT Center for Continuous Manufacturing (CCM). The meeting is motivated by FDA CDER Janet Woodcock to open up CCM vision to a wider industry view. The goal is to align on a five year vision for continuous manufacturing within the pharmaceutical industry. The morning session focused on technology implications of continuous manufacturing while the afternoon session centered on discussion of regulatory/quality issues. These notes reflect the discussion held during the meeting and should not be construed to represent consensus opinions of individuals or views of their organizations

The Novartis-MIT CCM was born in late 2007, has made much progress and included annual updates with FDA. The efforts have progressed from early research to the current scale-up phase with commercialization still to come.

What is Continuous?

Most attendees asserted early and longstanding involvement in continuous manufacturing, though this might mean only single unit operations. The CCM definition centers on flow via continuous end-to-end processes beginning with starting materials and producing drug product dosage units using a systems approach and developing an integrated control strategy. Themes include greater process understanding, systems approach, integrated process control, opening up areas of chemistry (e.g., via photochemical transformations) otherwise inaccessible via batch techniques, and eliminating "corrective" steps in drug product manufacturing (e.g., milling, granulation). Inherent in the ability to execute continuous processes are the requirements of Quality by Design (QbD). Skid mounted continuous units, even transportable, were emphasized as was the desirability of establishing standards for interfaces between unit operations to enable plug and play as well as interchangeability of equipment between suppliers.

Barriers to Implementation:

Most agreed that there are huge gains once the transition of infrastructure to continuous is complete. At least one company views the initial move to continuous technology as a strategic R&D investment analogous to investments made in new molecular entities. However, at most companies, justification of the initiation of the transformation in the current corporate environment is the primary impediment to implementation of continuous manufacturing projects. A graphic example of the lack of progress in pharmaceutical manufacturing was illustrated via the story of showing photographs of 1960s era automobile assembly lines and a current, state-of-the-art auto assembly line compared to a photograph of a 1960s era drug manufacturing plant and a new, state-of-the-art but almost identical appearing drug plant. Limited implementations of continuous technology have been justified based on very high volume, very fast reactions, or safety concerns. Suppliers such as CMOs generally lack any continuous manufacturing capability and often show no interest in adopting continuous technology or will do so only at significantly higher prices

(2X). Precise quantification of benefits remains elusive. Paradoxically, the move away from the blockbuster model of drugs may enable continuous as existing large volume kit is irrelevant, and new infrastructure investments will need to be made anyway. Opportunities lie in small volume drugs, since the existing capital infrastructure does not fit this realm.

In addition to the alternative view of the transformation effort as a strategic investment similar to drug R&D investments, some companies are developing platform/portfolio justifications for continuous manufacturing investments. Inn addition, implementation of a "hybrid" process combining batch and continuous operations allows some to begin to gain experience and comfort with the technology while delivering an excellent return on investment. Nevertheless, for many firms, drivers include Quality gains as well as inventory reductions, real time release, and faster response times (even make to order processes). It is important to have a corporate sponsor.

Benefits of Continuous:

The value of true end-to-end integration versus separate API and DP continuous streams was discussed. The biggest gain is achieved via end-to-end as one optimizes the entire process by focusing on the shortest path from starting material to finished product as opposed to today's norm of squeezing into existing infrastructure. One needs to rethink an entire process, not just convert each separate unit operation to continuous. In continuous processes the volume moving at any moment is much smaller with concomitant advantages for equipment scale, safety, risk, etc. On the other hand, nowhere near as complete a CMC development toolbox (process and analytical) exists yet for continuous operations. There was advocacy for starting the R&D to build a new toolbox as well as to implement via plug and play strategy as hybrid approaches mixing batch and continuous will be sub-optimal. In addition, involving corporate R&D early is important, since the transition to continuous methods cannot be driven entirely by Manufacturing. Another stratagem for encouraging the transition to continuous is to start in Discovery and Development. If NMEs are developed from the beginning with continuous technology, then it enhances the likelihood of adoption during later stages.

From a regulatory viewpoint, recent changes to US clinical regulations allowing accelerated paths for breakthrough therapies could force CMC development onto the critical path to approval and launch. This should force pharmaceutical companies to re-examine the CMC development/implementation pathway at least for the subset of molecules that are substantially better medicines. To some extent this reinforces the shift to more frontend-loaded process development begun during implementation of PAT and QbD concepts.

Precompetitive collaboration possibilities:

There was advocacy for enhanced pre-competitive collaboration to attain critical mass of resources. There was somewhat less clarity regarding what areas made

sense to explore. Many companies no longer value process patents. Innovator companies focus on NME IP, so pre-competitive cooperation on continuous manufacturing may be viable especially if focused on platform technology areas. There was some pushback regarding the consortium concept as there is an argument that in a future of tighter margins, etc., manufacturing may become a source of competitive advantage as it is in many other industries. Also, previous histories with some unrelated consortia have been frustrating. On the other hand, there is an argument for establishment of industry-wide common platforms that enable equipment suppliers to respond and supply needed infrastructure components. While the suggestion to try to focus companies on a single project, possibly developing a humanitarian drug, seemed to lack traction, there seemed broad agreement to engage in information sharing regarding continuous. This was envisioned to include technical approaches to continuous manufacturing as well as business cases.

Similar challenges exist in continuous manufacturing of recombinant proteins including antibodies. Upstream processes and equipment are reasonably well developed; however, an issue is availability of equipment for continuous protein purification. Otherwise a robust approach has been designed that applies to orphan drugs as well as blockbusters and unstable as well as stable proteins.

Other industries that have made the transition to continuous have had to confront similar financial justification and technical challenges. However, being able to move away from the time consuming, expensive series of scale up development programs as a product is developed, launched, and grown offer significant payback. Nevertheless, it was admitted that certain leap of faith is initially required, for example, to commit to continuous spray drying. The importance of online characterization and elimination of secondary, statistically sampled inspections was stressed.

In addition, it is important to establish patient benefits from continuous manufacturing, for example, perhaps by enabling personalized dosing.

<u>Regulatory Aspects of Continuous Manufacturing of Pharmaceuticals:</u>
From a U.S. regulatory vantage, the desired state is clear: a robust and agile pharmaceutical manufacturing sector reliably producing high quality products with minimal regulatory oversight. (Citizens of the USA support the FDA through their taxes in order to minimize risks regarding drugs.) FDA has supported the development and implementation of continuous manufacturing processes since at least a 2001 – 2002 Advisory Committee. In addition, the FDA has supported importing advanced online/at-line monitoring and control strategies from other industries. Some note an apparent challenge to fit old regulations to these new concepts; however, the GMP regulations are written broadly, so the regulatory mechanisms are in place to accommodate the transition. On the other hand, it is admitted that the FDA is a “distributed” organization, so it is hard to implement cultural change quickly. The impending reorganization of CDER should help by

establishing two clear voices (versus many) on Pharmaceutical Quality, and some of the cultural questions will also be addressed via the reorganization. QbD and integrated control strategies enable continuous manufacturing, and further that the question shifts to companies to answer what is the risk of bad product? FDA will move to a more metrics-based, risk-based regulatory paradigm with realistic specification limits and evidence-based clinical outcomes decisions. In all, regulations will not be a barrier to implementation of continuous manufacturing. FDA will continue to focus on product quality while encouraging novel, non-traditional manufacturing processes and quality assurance systems.

Admittedly globalizing this view is another challenge. FDA can provide some leadership mainly through ICH as well as bilateral interactions such as via the FDA/EMA pilot program, but industry and academia have roles, too. They might lay a foundation by sponsoring scientific technical meetings and workshops that ultimately generate a white paper to propose standards for measuring/assuring quality in continuous processing and to spur ICH to action. The PAT implementation process was suggested as a model. There is an expectation of development of analytical technologies tuned for continuous manufacturing given the previously noted small mass (better sampling statistics) and decreased weight placed on spatial versus temporal homogeneity. The importance of implementation of "the right" analytical technology rather than process analytical technology for its own sake was also emphasized. This means both judicious selection of what technologies to apply at which stage in the development and manufacturing life cycle as well as the need to develop new methods to enable effective risk management of continuous manufacturing processes.

Successful implementation of continuous manufacturing demands increased process understanding, but it sometimes seems as if the more a company knows, the more Regulatory authorities ask regardless of any link to product quality. FDA's ONDQA is not industry's engineering department but on the other hand, companies do not always clearly communicate risks. There is an ongoing debate about the level of detail required of control systems in order to review CMC dossiers or GMP operations successfully. It was suggested that a small group start with a blank slate and consider based on previously mentioned regulatory principles, what should the regulatory paradigm be. For example, what does process validation mean in continuous processing? Of course, regardless of regulations, companies have a business decision as well regarding risk and how they assure themselves that their product is good. Stress testing and continuous monitoring are among the tools. The direction should be away from filing restrictive, highly detailed control system descriptions (inhibits continuous improvement especially for chemometric systems) in favor of showing regulatory authorities that one knows the risks and how they've been mitigated and showing that appropriate quality attributes are known and controlled through critical process parameters. Continuous process monitoring reinforces this, and FDA will look for results. Questions include is risk adequately mitigated at each stage of a continuous process? Do you know that you have the right stuff at each step? Are you continuously monitoring at each step? If you don't

know these and the overarching what are the risks and how are they mitigated, then you are back to the batch paradigm of testing in quality. In the end, a company owns process understanding while Regulatory authorities and the company own Quality and Risk.

Twelve Continuous Opportunities:

1. to invest in pre-competitive R&D targeted to platforms (establish "new norm");
2. to leverage the new breakthrough therapies regulations to develop new products more rapidly using continuous technology;
3. to develop continuous platform technology that can operate across multiple scales and doses (bring reality to personalized medicine);
4. to design new continuous processes according to QbD concepts to enable right-first-time and to avoid corrective steps;
5. to work with raw materials and equipment suppliers to develop new specification and new tools for continuous applications;
6. to reduce inventory;
7. to move toward a consensus for a dominant design around continuous manufacturing;
8. to collaboratively develop standards and to share platform data ultimately driving policy decisions;
9. to implement regulatory policies that encourage novel, non-traditional manufacturing processes and quality assurance systems.
10. to mitigate risk via smaller material mass volume and application of PAT;
11. to focus on the right analytical technology (rapid, enabling process decisions; new toolkit);
12. to change education, management, and mindset by developing academic-industry-regulatory education for continuous manufacturing based on principles and fundamentals and to translate this into management practice to evolve continuous manufacturing.

Executive Summary and Action Items

1. Implementation of continuous manufacturing into the pharmaceutical industry makes sense for a variety of reasons (costs, scale and scalability, safety, efficiency,…)
2. Regulations are not a significant impediment to this (and recent FDA changes to accelerate clinical development of breakthrough medicines may be a driver); however, financial justifications may be.
3. Toolkits need to be further developed for both unit operations (e.g., purification) and analytical/process monitoring methods.
4. Platform and non-proprietary information should be shared. MIT will collect information for dissemination. A larger conference on the discussion will be planned ultimately progressing to a workshop on regulatory and standards issues and likely a white paper with recommendations.