Achieving Continuous Manufacturing for Final Dosage Formation: Challenges and How to Meet Them May 20–21, 2014 Continuous Manufacturing Symposium

STEPHEN BYRN,[1] MARICIO FUTRAN,[2] HAYDEN THOMAS,[3] ERIC JAYJOCK,[2] NICOLA MARON,[4] ROBERT F. MEYER,[5] ALLAN S. MYERSON,[6] MICHAEL P. THIEN,[5] BERNHARDT L. TROUT[6]

[1]Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, Indiana
[2]Janssen Supply Group, LLC, 800 Ridgeview Drive Horsham, Pennsylvania
[3]Vertex Pharmaceuticals, Inc., 50 Northern Avenue Boston, Massachusetts 02210
[4]I.M.A. Industria Macchine Automatiche S.p.A., Via Emilia, 428-442. OZZANO DELL'EMILIA, 40064. Italy
[5]Global Science, Technology and Commercialization, Merck Manufacturing Division, Merck & Co., Inc., 770 Sumneytown Pike West Point, Pennsylvania
[6]Department of Chemical Engineering, Massachusetts Institute of Technology and Novartis-MIT Center for Continuous Manufacturing, 77 Massachusetts Avenue E19-502B Cambridge, Massachusetts 02139

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ABSTRACT: We describe the key issues and possibilities for continuous final dosage formation, otherwise known as downstream processing or drug product manufacturing. A distinction is made between heterogeneous processing and homogeneous processing, the latter of which is expected to add more value to continuous manufacturing. We also give the key motivations for moving to continuous manufacturing, some of the exciting new technologies, and the barriers to implementation of continuous manufacturing. Continuous processing of heterogeneous blends is the natural first step in converting existing batch processes to continuous. In heterogeneous processing, there are discrete particles that can segregate, versus in homogeneous processing, components are blended and homogenized such that they do not segregate. Heterogeneous processing can incorporate technologies that are closer to existing technologies, where homogeneous processing necessitates the development and incorporation of new technologies. Homogeneous processing has the greatest potential for reaping the full rewards of continuous manufacturing, but it takes long-term vision and a more significant change in process development than heterogeneous processing. Heterogeneous processing has the detriment that, as the technologies are adopted rather than developed, there is a strong tendency to incorporate correction steps, what we call below "The Rube Goldberg Problem." Thus, although heterogeneous processing will likely play a major role in the near-term transformation of heterogeneous to continuous processing, it is expected that homogeneous processing is the next step that will follow.

Specific action items for industry leaders are:

- Form precompetitive partnerships, including industry (pharmaceutical companies and equipment manufacturers), government, and universities. These precompetitive partnerships would develop case studies of continuous manufacturing and ideally perform joint-technology development, including development of small-scale equipment and processes.
- Develop ways to invest internally in continuous manufacturing. How best to do this will depend on the specifics of a given organization, in particular the current development projects. Upper managers will need to energize their process developers to incorporate continuous manufacturing in at least part of their processes to gain experience and demonstrate directly the benefits.
- Training of continuous manufacturing technologies, organizational approaches, and regulatory approaches is a key area that industrial leaders should pursue together.

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INTRODUCTION TO CONTINUOUS MANUFACTURING FOR FINAL DOSAGE FORMATION

As discussed in the Introduction of this volume, "continuous manufacturing" means integration, a systems approach, and a model-based control within a flow process. Thus, as a continuous process is designed as a whole, the distinction between upstream and downstream, or drug substance and drug product, as currently used, can be, potentially, eliminated. The disappearance of these terms corresponds to a change in mindset, which itself would lead to the adoption of new terms., There is, however, clearly still the need for expertise in chemical synthesis, reaction engineering and work-up on the one hand, and material understanding, formulation development, and formulation process engineering on the other. Here, we

Correspondence to: Bernhardt L. Trout (Telephone: +617-258-5021; Fax: +617-258-5042; E-mail: trout@mit.edu)

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focus on final dosage formation, including in this analysis the overlap between it and chemical synthesis, reaction engineering, and work-up. Although we cannot with certainty predict which technologies and technology strategies pharmaceutical manufacturers will adopt in the future, we do believe that the future can be very different than the current approach, and herein we outline the vision of continuous manufacturing for final dosage formation, the barriers to achieving that vision, and how the industry should work to overcome those barriers.

Although the technologies, and therefore development and manufacturing expertise, needed for the final dosage formulation aspects of continuous processing are different than those needed for chemical synthesis, reaction engineering, and work-up, there are many areas of overlap. These include crystallization, powder handling, solvents processing, process safety, and process monitoring and control technologies. In fact, as continuous manufacturing becomes more and more prevalent and new technologies come about, we expect that the various development and manufacturing specialties will tend toward convergence. There will still be various areas of expertise, but specialists will need to interact with other specialists much more than they do presently, in order to coordinate process development, and the differentiation among process development teams will become smaller and smaller. For example, the solvents for chemistry development will need to be chosen to take into account work-up, in addition to, at least for the last chemical step, processing aspects of final dosage formation, such as drying and mechanical properties. Furthermore, although we expect a transition period during which batch technologies are converted to similar flow technologies in which there will still be substantial in-process powder handling such that actives and excipients are processed heterogeneously, in the long run, we expect that the advantages of homogeneous processing will be such that most, if not all, continuous processes will involve homogenous processing technologies, in which actives and excipients are processed together. Homogeneous processing will necessitate new approaches to final dosage formation and corresponding new technologies, all of which will need to be integrated tightly with the other aspects of the process.

For these reasons, we term the subject of this white paper "final dosage formation," keeping in mind that in the world of continuous manufacturing terms like "upstream," "downstream," "drug substance," and "drug product" could be considered transitional terms, and may very well disappear. The focus here is on formation of tablets for oral dosage, but the reader will readily see how the approaches below can be used to produce alternative dosage forms, including films, liquids, depots, inserts, and implants.

HOW THE VISION OF CONTINUOUS PHARMACEUTICAL MANUFACTURING WILL CHANGE FINAL DOSAGE FORM OPERATIONS

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. Below, we discuss the trade-offs involved in dedicated final dosage form process trains versus multi-use process trains. We do envision minimizing, if not eliminating, powders handling, at least within the process itself—there will, most likely, still be the need for powder dosage into the process. In addition, even if processes do not achieve full continuous manufacturing as we have defined it, steps in that direction should prove to be of significant benefit across the industry, from brand Pharma companies to generics, from small-scale production to large-scale production, and from simple to complex formulations. Integration within a systems approach itself leads to a reduction of process steps, as the number of "correction" steps can be reduced or eliminated and in general processing steps can be streamlined. In batch processes, actives are almost always formed upstream into powders that typically do not have the properties needed for downstream. Thus, initial downstream steps typically include milling and blending. These can be streamlined in a continuous process. Furthermore, batch downstream steps often include granulation so that the mixture will have the properties needed for further processing, which is necessary because the mixture does not inherently possess the desired properties. Given that continuous manufacturing naturally encompasses more up front understanding, a continuous process would be designed and controlled such that the mixture has the desired properties engineered when it is made. Many of the batch upstream steps are not needed in continuous processing, particularly those at the interface of upstream and downstream. For example, crystallization and drying of the active might not be needed at all. Additionally, filling of the bulk active and transportation might not be needed, nor removal and dosing of the active, in downstream batch processing.

The continuous manufacturing plant could be capable of running constantly 24/7 for 50+ weeks/year, with no significant downtime for major cleaning (except in product or process changeover), as is the case in other industries ranging from foods to petrochemicals. For pharmaceuticals, such a process easily affords an annual production of 1 billion tablets, which translates to only 120,000 tablets per hour, a throughput that is typical of a single pilot-scale line using conventional technologies.

Because continuous processes are run under a constant state of control, dynamic aspects are minimized, and dynamics such as transients associated with start-up and shutdown can be controlled accurately so that products are within specifications all (or almost all) of the time. Along these lines, continuous processes are controlled using detailed process models, which themselves are used in advanced algorithms, leading to a much lower risk of going out of specification than batch processes. Because of in-line process analytical technology (PAT) tied to the control system, the dream of real time release becomes a reality in a natural way, as part of the process approach. And in the rare case of process perturbations, real-time rejection of small quantities of non-conforming product can be performed without sacrificing the defined batch. The processes themselves are more robust, leading to lower risk of stock-outs.

Furthermore, a manufacturing train for production of phase III clinical materials could be developed so that it is the commercial process, run for a short time for clinical supplies and year-round for commercial production. Thus, a scale-up step is skipped, allowing reduction of critical path timeline and reduced risk of development and manufacturing delays.

Heterogeneous versus Homogeneous Processing

We that expect that many, if not most, continuous processes that are developed in the near future will be "heterogeneous processes." These are processes in which the components tend