



Opportunities for Standardization in Continuous Manufacturing

March 23rd, 2017

Robert Femia, Ph.D.
Senior Vice President-Chemical Medicines
Global Science and Standards Division

Opportunities for Standardization in Continuous Manufacturing - Overview

- ▶ Pharmaceutical Continuous Manufacturing (PCM) has been identified as a National Priority Technology.
 - In the interest of exploring this technology, USP held a roundtable discussion among industry, academia, and regulatory experts on the field in June of 2016.
 - USP involvement in this topic is consistent with our mission statement:
 - To improve global public health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.
- ▶ The roundtable identified numerous areas of opportunity for standardization in Continuous Manufacturing.

Opportunities for Standardization in Continuous Manufacturing - Overview

USP Convention Resolution 2:

USP will meet the needs of U.S. Food and Drug Administration (FDA), industry, and other stakeholders for modern monographs within USP–NF.

USP will work to:

- **eliminate the existing backlog of monographs in need of modernization, and**
- **proactively evaluate and update monographs to maintain their relevance given scientific advances and evolving manufacturing and regulatory approaches.**

USP will work with industry and FDA to explore new strategies for sharing analytical methods and specifications needed to modernize monographs.

Opportunities for Standardization in Continuous Manufacturing - Overview

The possibility of standards development in Pharmaceutical Continuous Manufacturing also fits in with USP-NF's Convention Resolutions.

Specific areas of opportunity will be discussed today as well as recent USP activity in this discipline.

Pharmaceutical Continuous Manufacturing (PCM) has been identified as a National Priority Technology

- ▶ Over the last 5 years, pharma and biotech firms have been updating their manufacturing technologies and facilities.
- ▶ Industry leaders are showing confidence that PCM is an area of significant potential improvement, with benefits including faster development timelines, better quality products, less scale-up risks and long-term economic advantages.
- ▶ FDA has committed to assist with the build up of manufacturing competency, urging pharma to get on board with PCM.
- ▶ Product approvals for PCM based processes have already been given, with more on the horizon.
- ▶ Main stream pharma manufacturers including all of the first tier companies like Pfizer, Merck, Eli Lilly, GSK, BMS, and J&J are already well on the path to adopt continuous production of API and/or finished products through the use of PCM.

Pharmaceutical Continuous Manufacturing (PCM) has been identified as a National Priority Technology –cont.

- ▶ Contracting manufacturing organizations(CMO), generics manufacturers, and smaller pharma players in emerging markets (India, China, and others) are also showing great interest in PCM, and are establishing their own capabilities from facility and staffing perspectives.
- ▶ The interest in PCM is also supported by the rapidly increasing number of public activities, such as PCM focused international conferences and workshops:

Year	2012	2013	2014	2015	2016
PCM focused int; conferences& workshops	0	2	3	6	15

USP Round Table Discussion on Opportunities for Standardization in Continuous Manufacturing.

► Objectives:

- Provide an **open platform** to share knowledge of pharmaceutical continuous manufacturing (PCM) and insights on the possible future role of quality standard in this arena.
- Convene an **interactive discussion** on key technological and quality challenges in PCM.
- Identify **scientifically sound, novel technologies and control strategies** that will enable and grow PCM to improve drug quality and produce medicines that are consistently safe and effective.
- Build a **technology and quality roadmap** for accelerating development, implementation, and standardization of PCM.

- ▶ The need for feed-forward controls in addition to feedback controls
- ▶ Performance specifications and strategies for the use of real-time release testing.
- ▶ Need for more robust/specific characterization of excipients used in PCM, particularly with regard to characterizing material variability, and use of specific analytical techniques.
- ▶ Identification of appropriate analytical tools for material characterization.
- ▶ Cleaning and reassembly of equipment
- ▶ Close partnership with FDA on framing approval guidelines.
- ▶ Growth in need for process engineers (Training/Standard Approaches)
- ▶ Requirements for standardization of processing terms across the industry.
- ▶ Definition of what constitutes a deviation when the process controls allow for feedback and feed forward control of product attributes when changes in material characteristics in process occur.
- ▶ Scale-up and validation

- ▶ USP will develop a program for bringing opportunities identified into the standardization process.

- ▶ Immediate Next Steps identified following the Round Table discussion:
 - USP would form an Expert Panel: “Quality Standards for Pharmaceutical Continuous Manufacturing”
 - Develop Collaboration/Partnership relationships with critical stakeholders such as FDA, Industry, and Academia experts in the field.
 - Explore research and training collaboration opportunities with PCM research centers
 - Develop Educational CM Workshop for the progression of training and dialogue on this topic.

- ▶ Across all topics identified through the Round Table discussion, pharmaceutical continuous manufacturing (PCM) provides an opportunity for consistent and broad access to better quality medicines at reduced costs.

- ▶ The **Quality Standards for Pharmaceutical Continuous Manufacturing Expert Panel** would be a Joint Expert Panel intended to provide recommendations outlining the development and implementation of compendial quality standards for PCM.
- ▶ This joint Expert Panel would be overseen by:
 - ▶ General Chapters Chemical Analysis Expert Committee (lead EC)
 - ▶ General Chapters Physical Analysis Expert Committee
 - ▶ General Chapters Dosage Forms Expert Committee

Initial Objectives of Expert Panel:

- ▶ Prepare and publish in Pharmacopeial Forum an initial stimuli article, which will serve as a framework for development of a General Information Chapter for PCM.
- ▶ Based on the panel discussions and public inputs, identify and create a list of topics on potential USP Standards related to PCM.
- ▶ In line with the compendial process, this may be followed by additional stimuli articles addressing topics raised during public commentary.
- ▶ Develop a General Information Chapter(s) on PCM and publish in Pharmacopeial Forum.

Initial Objectives of Expert Panel (continued):

- ▶ Address the public comments on the General Information Chapter and decide either to revise the proposal and republish in PF or finalize the proposal and publish.
- ▶ Address any needs identified around developing General Tests and Assay Chapters on the following topics to include, but not limited to:
 - ▶ Material Properties
 - ▶ Analytical techniques/instrumentation
 - ▶ Statistical methods around finished product release

► **Chair:** Nuno Matos Continuous Manufacturing R&D, Hovione

► **Members**

- | | |
|-------------------------------|-------------------------------------|
| 1. Shaukat Ali, Industry | 10. Kimberly Lamey, Industry |
| 2. Ahmad Almaya, Industry | 11. Fernando Muzzio, Academia |
| 3. Thomas Garcia, Industry | 12. William Randolph, Industry |
| 4. Doug Hausner, Academia | 13. Mark Schweitzer, Industry |
| 5. Eric Jayjock, Industry | 14. Raymond Skwierczynski, Industry |
| 6. Keith Jensen, Academia | 15. Kelly Swinney, Industry |
| 7. Johannes Khinast, Academia | 16. Bernhardt Trout, Academia |
| 8. Pramod Kotwal, Industry | 17. Amy Walia, Industry |
| 9. Marcus Krumme, Industry | |

► **Government Liaisons:**

Celia Cruz, FDA

Thomas O'Connor, FDA

- ▶ The Expert Panel held its first meeting in January of 2017.
- ▶ The following topics were identified for immediate action:
 - A sub-team of the panel will work on standardizing the terminology used in different venues related to pharmaceutical manufacturing by reviewing the literature and available documentation and compiling a glossary of terms. The final document will be published in Pharmacopeial Forum as a “Stimuli Article” for public input.
 - Another sub-team will work on identifying and compiling the materials properties and attributes of the starting materials and in-process materials which most impact a continuous manufacturing process and the quality of the final products.
 - The panel will also address the possibility of standardization for the on-line measurements procedures which would enable comparison of data between different PCM production lines.

Other Areas of Engagement for Chemical Medicines Expert Panel Include:

The Expert Panel agreed with initial opportunities identified by the Round Table Discussion and will take on the following challenges moving forward:

- ▶ Control strategy standardization
- ▶ Ingredient characterization standardization (monograph and reference standard)
- ▶ Product release standardization
- ▶ Equipment/system requirement standardization
- ▶ Sensing technology standardization
- ▶ System modeling standardization
- ▶ Other TBD

What we believe that the USP Continuous Manufacturing EP can contribute the implementation of PCM:

- ▶ Establish standard requirements for Manufacturing Development, Approval, and Maintenance.
- ▶ Drive standard processes on system development, control strategies, process analytical, and product release including sampling plans, hold times, design space requirements, real time release standards etc.
- ▶ Unify standardization efforts from several consortia and professional organizations.
- ▶ Help driving equipment harmonization towards standardized modular design and interchangeable unit operations.
- ▶ Foster cooperation across industry/academia/regulators, and stimulate knowledge sharing.



Global Expertise
Trusted Standards
Improved Health



A faint, light gray world map serves as the background for the "Thank You" text. The map shows the outlines of all major continents.

Thank You