Implementation of ICH Q13 Continuous Manufacturing Guidance

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Presentation Outline

- Continuous Manufacturing (CM) Basics
- ICH Q13 Guidance
- FDA Experience
- Future Directions and Enabling CM of Generics
- Conclusion

Continuous Manufacturing (CM) Basics

CM Basics

- Continuous feeding of input materials into, the transformation of in-process materials within, and the concomitant removal of output materials from a manufacturing process.
- ICH Q13 focuses on the integrated aspects of a CM system in which **two or more** unit operations are directly connected

Quality

- Amount of material processed at any instance is small compared to batch processes
  - Minimal spatial quality variability
- Desired quantity/batch size obtained through continuous processing over time
  - Potential for time-based variability; need to maintain a state of control
  - Ease of batch size variation (no equipment change)

State of Control

- ICH Q10 definition
  - A condition in which the set of controls consistently provides assurance of continued process performance and product quality
- The control strategy in CM aims to maintain a state of control over the run time

Control Strategy

- Knowledge of process dynamics
  - Residence time distribution (RTD) characterization
  - Helps understand impact of disturbances and interactions of connected unit operations
  - Facilitates material traceability and diversion, and advantage offered by CM
    - Together with a sound IPC strategy

ICH Q13 Guidance

Continuous Manufacturing Journey

- Potential to improve the quality, efficiency, agility, and flexibility of drug substance and drug product (DS/DP) manufacture.

Harmonization

- Initial industry concern regarding CM:
  - Lack of international harmonization
  - However, insufficient experience for an ICH guideline

2018 ICH Q13 Proposal - Drivers

- Academia support and demonstration of feasibility
- CM publications
- July 2015 FDA approval of Orkambi (for cystic fibrosis)
- Support from key international regulatory authorities
  - Development of internal documents

COMMENTARY

Regulatory and Quality Considerations for Continuous Manufacturing May 20–21, 2014 Continuous Symposium

GRETCHEN ALLISON,[1] YANXI TAN CAIN,[2] CHARLES COONEY,[3] TOM GARCIA,[4] TARA GOOEN BIZJAK,[5] OYVIND HOLTE,[6] NIRDOSH JAGOTA,[7] BEKKI KOMAS,[8] EVDOKIA KORAKIANITI,[9] DORA KOURTI,[10] RAPTI MADURAWE,[5] ELAINE MOREFIELD,[11] FRANK MONTGOMERY,[12] MOHEB NASR,[13] WILLIAM RANDOLPH,[14] JEAN-LOUIS ROBERT,[15] DAVE RUDD,[9] DIANE ZEZZA[16]

J Pharm Innov
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REVIEW ARTICLE

Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

Sau L. Lee · Thomas F. O'Connor · Xiaochuan Yang · Celia N. Cruz · Sharmista Chatterjee · Rapti D. Madurawe · Christine M. V. Moore · Lawrence X. Yu · Janet Woodcock

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

ELSEVIER

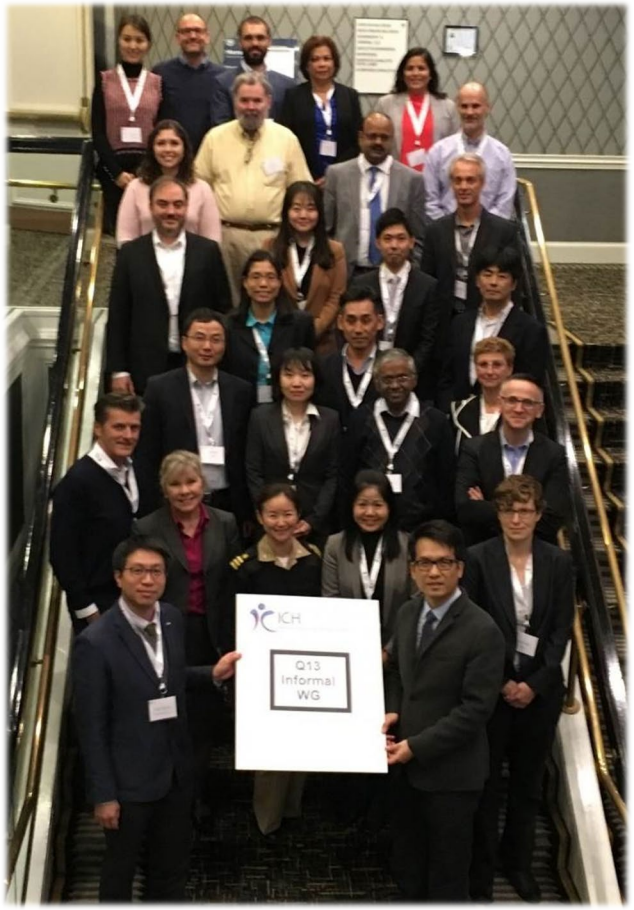
Special Topic Commentary

Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving From Theory to Practice: September 26-27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals

Moheb M. Nasr [1,*], Markus Krumme [2], Yoshihiro Matsuda [3], Bernhardt L. Trout [4], Clive Badman [5], Salvatore Mascia [6], Charles L. Cooney [4], Keith D. Jensen [4], Alastair Florence [7], Craig Johnston [7], Konstantin Konstantinov [8], Sau L. Lee [9]

Scope/Objective of ICH Q13

- Concept Paper and Business Plan (11/2018)
  - DS/DP small molecules and therapeutic proteins; new and existing products
  - Key CM-specific technical and regulatory considerations that promote harmonization
  - Flexible approaches to develop/implement CM
  - Guidance to industry and regulatory agencies regarding regulatory expectations



Q13 Strategy

Main Body of the Guideline

- Fundamentals; not modality specific
- Sufficient detail, flexible approach
- Scientific considerations
- Harmonized regulatory considerations, including CTD and CGMP topics

Annexes

- Specific modalities with illustrative examples
  - I – Small molecule DS
  - II – Small molecule DP
  - III – Protein DS
  - IV – Integrated DS & DP (small molecule)
  - V - Disturbances

ICH Q13 Discussions

Scientific

- State of Control
- Process Dynamics
- Material Characterization/Control
- Equip. Design/System Integration
- Process Monitoring and Control
- Material Traceability and Diversion
- Process Models
- Changes in Production Output

Regulatory

- Description of Manufacturing Process
- Process Controls
- Control Strategy
- Batch Description and Batch Size
- Process Models
- DS and DP Stability
- Conversion of a Batch Process to CM
- Process Validation

Finalization

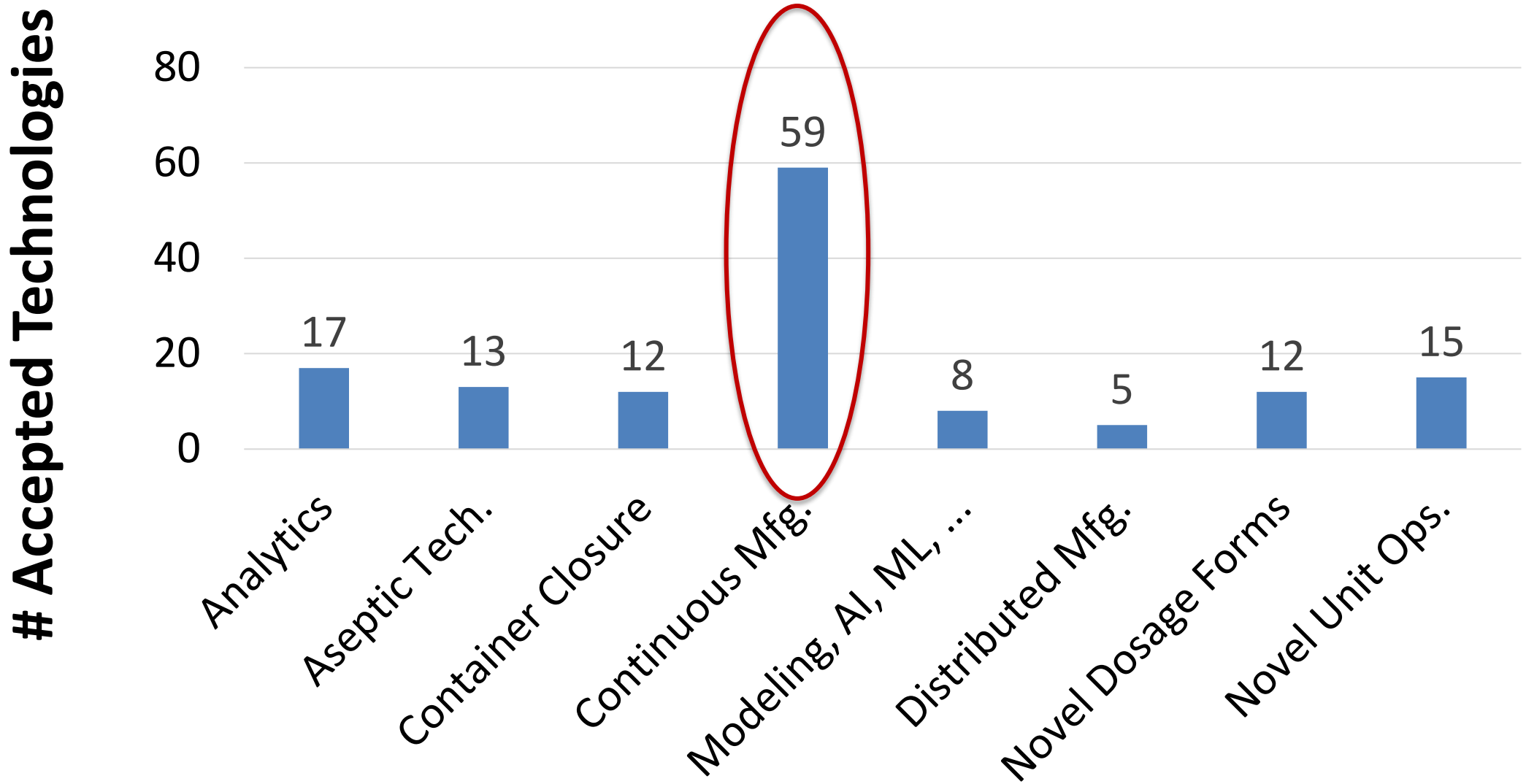
- November 2022: **Step 4 achieved; ICH Q13 finalized**
- January 2023: **ICH Q13 Implementation Working Group (IWG) established** to develop training materials

Current ICH Q13 Status

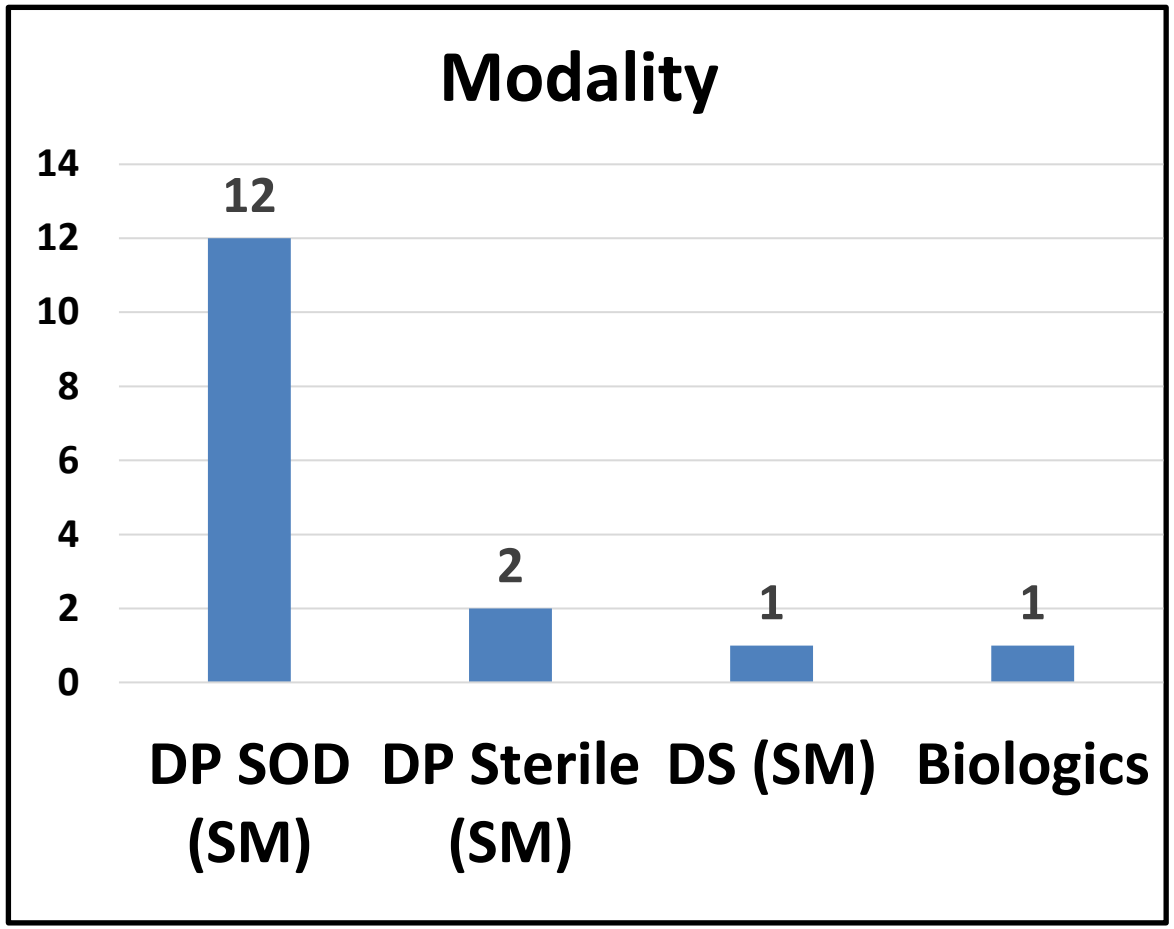
- Training materials are under development
  - More details and examples to aid implementation
  - Narrated online slides and videos. Several topics
    - Batch definition, Control strategy development, Residence time distribution (RTD), Disturbance management, Stability data, RTD/process models, etc.
- 2024: Target completion and training roll-out

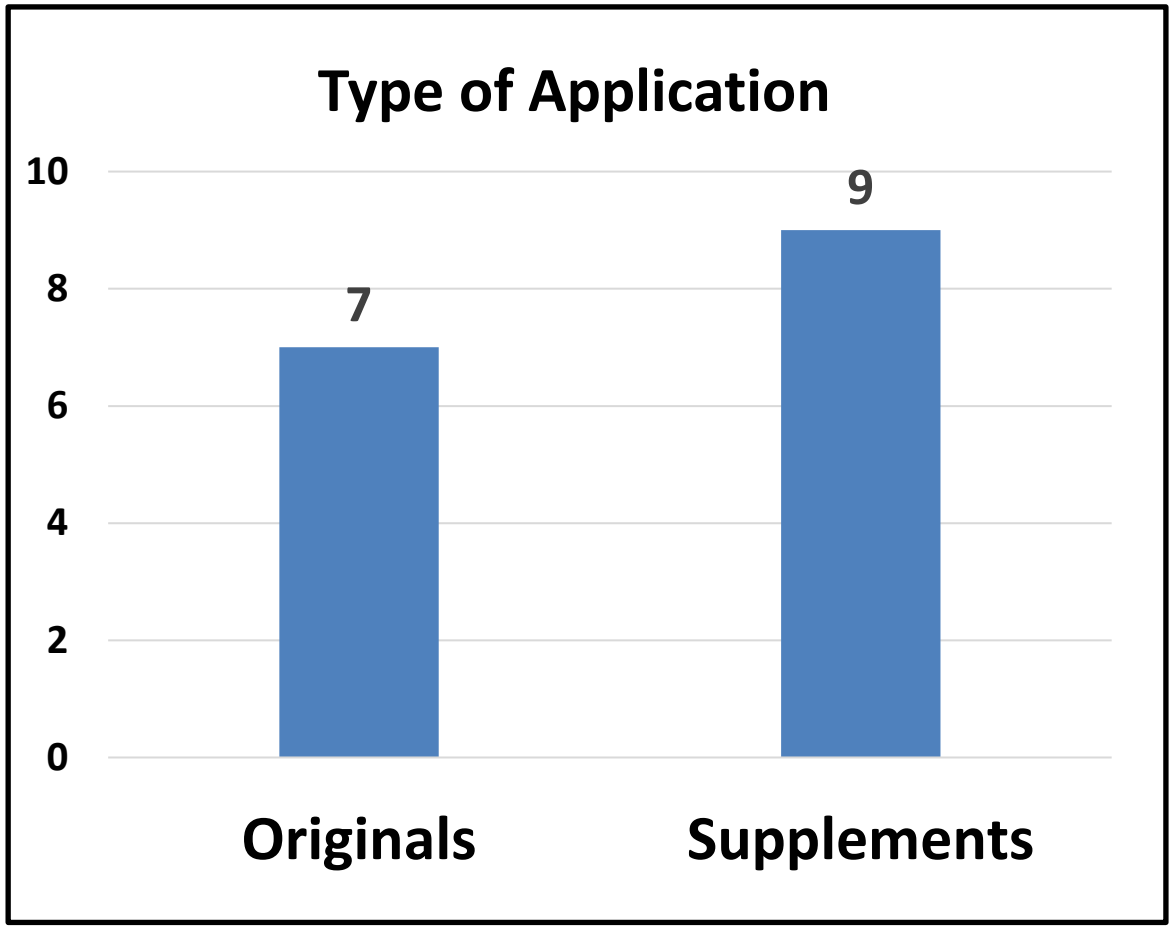
FDA Experience

CDER Emerging Technology Program



Approved CM Submissions





SM – small molecule SOD – solid oral dosage
DP – drug product DS – Drug Substance

FDA Experience

- Increased knowledge, FDA research and staff trainings
- Continuous Direct Compression (CDC) graduated from ETP
  - CDC with novel control strategies still under ETP
- No delay in approval of CM, no “regulatory burden”*
  - Including priority, breakthrough and supplement goal dates
  - Facilitators: ETP site visits (pre-submission), Pre-approval inspections (PAI) and information requests (IR)
  - Ease of 2nd CM application for both industry and FDA

*International Journal of Pharmaceutics Volume 622, 25 June 2022, 12177

Observations

- CM with other advanced manuf. approaches
- Increased interest in CM of biotech products
- Need for robust PAT tools and IPC methods
- Better utilization of ‘high-volume’ data
- CM is not yet mainstream

Future Directions and Enabling CM of Generics

CM and Generics

- Increased adoption of CM would lead to lower costs (*Rossi, CV., J. Ph. Innov., Jan 22*)
- Slow adoption by Generics. Untapped advantages
  - Improved quality - Batch size flexibility,
  - Intact supply chain - Less drug shortages
  - Ease of stability batch manufacture
  - Rapid development (once CM experience gained)

Advancing CM Further

- Making a strong business case. Engaging business decision makers
  - Translate CM benefits to measurable business metrics
  - Understand when the CM business case is stronger than for batch
  - Understand short-term vs. long-term benefits
  - Need business case examples from Industry
- Explore avenues for decreasing the cost of CM adoption

Facilitating CM of Generics

- CM capable/experienced CMOs
- CM as a platform technology
  - CDC platform an easy win
- Drug Master Files (DMF)
- Use of standardized equipment, automation
- Development (and assessment) per ICH Q13

Conclusions

- Finalization of the harmonized ICH Q13 CM guidance underscores that there are no regulatory barriers to the adoption of CM
- Collaborative efforts from Industry, Academia and Regulators have resulted in increased knowledge and approval of CM processes in multiple regions
- CM is currently the most advanced '*advanced manufacturing technology*.' However, the adoption of CM is still limited
- There is a need to make a sound business case and engage decision makers on the value/benefits of CM technology

U.S. FOOD & DRUG ADMINISTRATION

Thank You!