Technological Innovation in Manufacturing

Thomas O’Connor, Ph.D.
Office of Pharmaceutical Quality
US FDA Center for Drug Evaluation and Research
IPA 5th Advanced GMP Workshop
November 5th, 2020
Disclaimer

This presentation reflects the views of the authors and should not be construed to represent FDA’s views or policies.
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.
Patients expect safe and effective medicine with every dose they take.
Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects.

www.fda.gov
It is what gives patients confidence in their next dose of medicine.
What is Advanced Manufacturing?

- Novel **manufacturing methods** to improve process robustness and efficiency
- Novel **dosage forms** or delivery systems to improve drug delivery and targeting
- Novel **analytical tools** to improve product quality testing, process monitoring and/or control
Advanced Manufacturing

Our vision is to achieve “a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.” Janet Woodcock MD, Director, CDER FDA

Advanced manufacturing can improve drug manufacturing and help ensure that quality medicine is available.

**Produce better quality medicine.** A transition to advanced manufacturing technology can facilitate operation above a six-sigma level, meaning manufacturers would see no more than 3.4 defects per million opportunities.

**Develop drugs rapidly.** Advanced manufacturing technology speed the development of novel or patient-focused therapeutics (e.g., orphan drugs, oncology drugs, breakthrough therapies).

**Prevent drug shortages.** FDA found 62% of drug shortages were associated with manufacturing or quality problems. Advanced manufacturing can proactively reduce today’s quality-related manufacturing issues.

**Improve emergency preparedness.** More agile and flexible manufacturing technology can help manufacturers pivot quickly to address unanticipated demands in a public health emergency.
CDER Efforts in Advanced Manufacturing
Emerging Technology Program
US FDA Center for Drug Evaluation and Research
Encourage and support the adoption of **innovative technology**
to modernize pharmaceutical development and manufacturing
through **close collaboration** with industry and other relevant stakeholders
A small cross-functional Emerging Technology Team (ETT) with representation from all relevant FDA quality assessment and inspection programs (CDER/OPQ, CDER/OC & ORA)
Program Objectives

To ensure consistency, continuity, and predictability in assessment and inspection

To provide a forum for firms to engage in early dialogue with FDA to support innovation

To serve as a centralized location for external inquiries on novel technologies

To engage international regulatory agencies to share learnings and approaches

To facilitate knowledge transfer to relevant CDER and ORA assessment and inspection programs

To identify and evaluate potential roadblocks relating to existing guidance, policy, or practice

To help establish scientific standards and policy, as needed

Contact us: CDER-ETT@fda.hhs.gov
ETT Collaborative Approach

Over the course of an ETP project, ETT may employ a combination of early engagement, ET site visits, integrated quality assessments or Pre-Approval Inspections.

The same ETT representative(s) will be involved in the entire process.

The composition of an assessment team will likely remain the same throughout the entire process.
Progress in Emerging Technology

Approval of a first regulatory application utilizing 3D printing technologies

Approvals of applications utilizing continuous manufacturing (CM)
• Small molecule drug product and drug substance
• Automated semi-continuous sterile manufacturing

Requests accepted to the ET program since launching in late 2014
• Received over 100 ETT proposals and accepted ~50% of these proposals to the program
Getting Ready for ETT Meetings

Regulatory Agencies
- Willing to learn / understand and recognize potential of new technologies with an open mind
- Make science- and risk-based assessments and decisions
- Be transparent to industry and not afraid to ask questions
- Multi-disciplinary approach (collaborative)

Industry
- Be transparent and willing to share with the agency early
- Not afraid to receive and answer many questions from the agency
- View regulators as part of your team

Right Mindset and Culture

We are getting there!
For ETT Activities visit the ETP website:
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm523228.htm
FDA Experience: Emerging Technologies

- CM of drug substance
- CM of drug product
- End-to-end CM
- Pharmacy-on-demand
- Model-based control strategy for continuous manufacturing
- Continuous aseptic spray drying
- 3D printing manufacturing
- Ultra long-acting oral formulation
FDA Experience: Emerging Technologies

- Controlled ice nucleation for lyophilization processes
- Comprehensive product testing using a single multi-attribute assay (multi-attribute method)
- Continuous manufacturing for a downstream process
- End-to-end integrated bioprocess
- Pharmacy on demand (small manufacturing platform for continuous bioprocesses)
FDA Experience: Emerging Technologies

- Distributed Manufacturing
- Closed aseptic filling system
- Isolator and robotic arm for aseptic filling
- Novel container and closure system for injectable products
FDA Science and Research Activities: Emerging Technology

OPQ Science and Research

- Process modeling and simulation
- Multi-attribute methods
- Controlled ice nucleation
- Characterization of novel glass designs
- In-house laboratory capability for advanced manufacturing technologies
- High throughput analytical approaches
- Emerging Therapies (oligonucleotides)
Emerging Technology Program:
1) Continuous Manufacturing
2) Industry 4.0: Advanced Process Control and Modeling
3) Distributed Manufacturing
Continuous Manufacturing

- CDER approved six applications utilizing continuous manufacturing for finished dosage form manufacturing, one application utilizing it for a top-selling API, and semi-continuous process for sterile injectable manufacturing.
- Standards: International standards (e.g., USP, ASTM) and regulatory guidance (FDA draft guidance, ICH Q13 Working Group) for CM are being formulated.
- Continuous API manufacturing characterized by diversity in unit operations and process sequence configurations.
- Manufacturing process configuration:
  - Isolated continuous and batch unit operations (e.g., continuous flow reactors)
  - Integrated continuous unit operations and isolated batch unit operations

Continuous Flow C-Glycosylation via Metal-Halogen Exchange: Process Understanding and Improvements toward Efficient Manufacturing of Remdesivir

  - Better synthetic routes, and new capabilities
  - Improved Health, Safety, and Environmental performance
Continuous Synthetic API Manufacturing

• Telescoped reactions
  – Can lead to complex reactions with many different species in the mixture
• Integrated process lines often contain surge capacity that decouple segment of the process train
• Process monitoring approach is a common ETT-Industry discussion area
  – In process controls may combine process parameter limits with a specified duration (e.g. outside of +/- 10% for 20s)
  – Specify context of use of PAT in the control strategy
• Process robustness: solids may be present in the reaction as reagents, intermediates, byproducts, or as the product causing process disruptions

Vapourtec Flow Chemistry System
Emerging Digital Tools and Technologies in Pharmaceutical Drug Manufacturing

Cloud/Edge Computing
Internet of Things
Process Analytics
Big Data/Data Visualization
Artificial Intelligence
Machine Learning
Digital Twins
Automation and Robotics Pharma 4.0
Block Chain

What is the Scope for Product Quality?
Digital Twins: Modeling and Simulation

- Advanced manufacturing a potential driving force for utilization of process modeling
- Modeling approaches evolving in the pharmaceutical industry (e.g. digital twins)
- Models can facilitate risk assessment, improve process design, and improve process performance through online monitoring and control
  - Predictive models have appeared in regulatory submissions
  - FDA has developed internal process modeling and simulation capability
- Technology Specific Considerations
  - Model categorization considering purpose, impact and risk
  - Exploring utility of risk-based model validation assessment frameworks
  - Model maintenance plans over product lifecycle

https://doi.org/10.1016/j.compchemeng.2019.06.033
Advanced process control is an umbrella term for a range of techniques that are implemented within industrial process control systems. APC is usually deployed optionally and in addition to basic process control.

Advanced process control could facilitate achieving 6σ quality for some processes.

Two enablers for APC:

- Measurement of process outputs
- Product and process understanding that could be used to adjust process to maintain a uniform output

Distributed Manufacturing (DM)

- *Distributed Manufacturing (DM)*: is a decentralized manufacturing platform that is coordinated by one management, is mobile, and can be deployed to multiple locations.
  - DM typically comprises of pre-fabricated, mobile, modular manufacturing/testing units
  - Oversight is established by centralized QA, execution of manufacturing occurs where the unit is deployed
Use Cases for DM Discussed with ETT

Expanding capacity at a given facility
- Implementing POD within existing facility

Mobile
- Relocating PODs between existing facilities

Cloning
- Replicating PODs to increase capacity

Response to Public Health
- Moving POD to point of care/ emergency response

Courtesy D. Powers G-CON
Acknowledgements

Emerging Technology Team

OPQ Leadership

Industry Partners
Thank You!