

Fostering Innovation through Collaboration

Presented by:

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Learning Objectives

- Explain advanced manufacturing important for both FDA and pharmaceutical industry
- Describe CDER's efforts to support the implementation advanced manufacturing for pharmaceuticals
- Describe how OPQ's research has impacted CDER's assessment of Emerging Technologies



The Importance of Advanced Manufacturing

US FDA Center for Drug Evaluation and Research

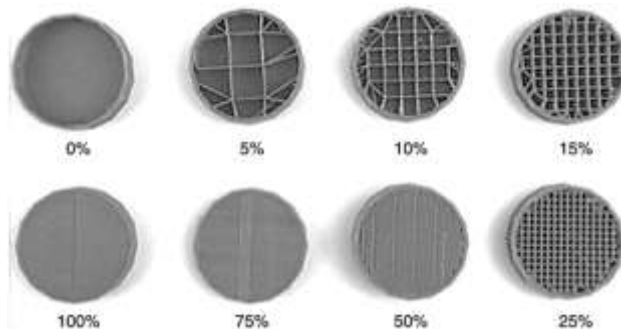
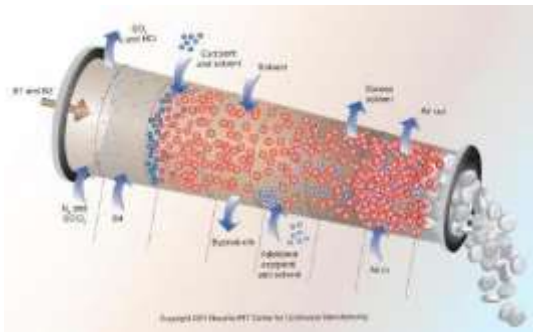
Pharmaceutical Manufacturing Compared to Other Manufacturing Industries



- Lower overall equipment effectiveness
- Lower first pass yield – zero defects
- Longer production lead time
- Larger inventories of finished products
- Lower direct to indirect labor ratio

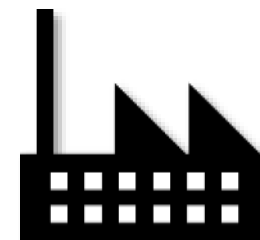
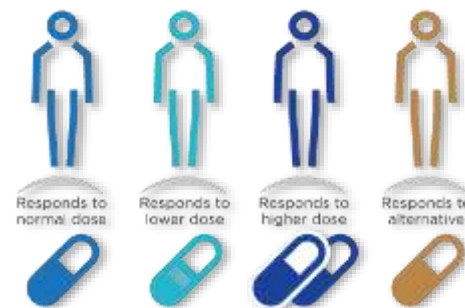
What is Advanced Manufacturing?

- 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



Why is Advanced Manufacturing important for both FDA and pharmaceutical industry?

- **Addresses the underlying causes of drug shortages**
 - Helps mitigate or prevent future production problems
- **Facilitates new clinical modalities**
 - Precision and individualized medicines
 - A wider range of novel dosage forms and doses - without extensive alterations of the process
 - Convenient fixed-combination dosage forms
- **Improves manufacturing efficiency**
 - Increase process robustness
 - Lower manufacturing costs
 - Increase supply chain flexibility



Generic Industry and Advanced Manufacturing

- Advanced manufacturing can provide benefits to the generic drug industry
- CDER's Emerging Technology Team is working with sponsors to implement advanced manufacturing for generic products
- There are challenges to implementation though:
 - Adoption of emerging technology requires new investment
 - Changing inventory of products being manufactured (platform technologies)
 - Development of new knowledge and skills

Through Collaboration can Overcome these Challenges
and Foster Innovation



CDER Efforts in Advanced Manufacturing

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A close-up photograph of a person's hands. The left hand is holding an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the right hand. The background is blurred, showing a person's face and clothing. The text "Emerging Technology Program Science and Research" is overlaid in white with a black outline.

Emerging Technology Program Science and Research

Emerging Technology Program

US FDA Center for Drug Evaluation and Research



Mission

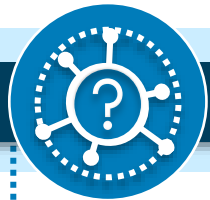
Encourage and support the adoption of **innovative technology** to modernize pharmaceutical **development and manufacturing** through **close collaboration** with industry and other relevant stakeholders



Team

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 serve as a centralized location for external inquiries on novel technologies



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



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



To engage international regulatory agencies to share learnings and approaches



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



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



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



Getting Ready for ETT Meetings



Right Mindset and Culture

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



**We are
getting
there!**

For ETT Activities visit the ETP website:

<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm523228.htm>



Science and Research

US FDA Center for Drug Evaluation and Research

OPQ Research and Emerging Technology Program

- Knowledge gained from the internal and sponsored research inform policy, assessment, and inspection activities, ensuring that FDA regulatory policies reflect state-of-the-art manufacturing science.

Collaborations allow OPQ to leverage external expertise and capabilities to address scientific issues

**OPQ
Labs**

Industry

Shared Learning and Open Communication to Accelerate
Adoption of Emerging Technologies to Advance Product
Quality



Examples of Advanced Manufacturing

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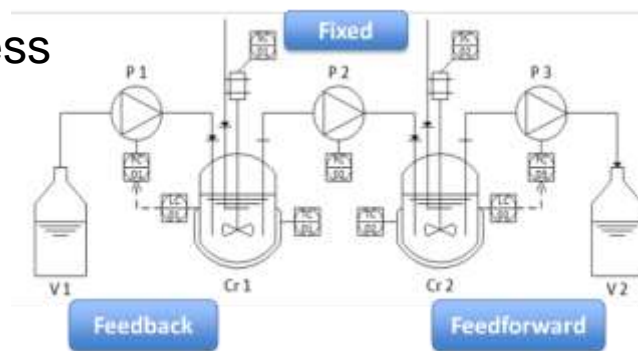
Case Study #1: Continuous Manufacturing of APIs

Question: What are appropriate science and risk based questions in-process controls for ensuring process performance and product quality?

- Driving forces for continuous manufacturing of APIs
 - Enabling new chemistries
 - Improved safety
 - Improved quality assurance
 - Cost savings
- Characterized by diversity in unit operations and process sequence configurations
 - Integrated process lines often contain surge capacity that decouple segment of the process train
- Process monitoring needed to detect transient disturbances
- Solids may be present in the reaction as reagents, intermediates, byproducts, or as the product
 - Clogging can impact product performance and potentially product quality



Vapourtec Flow Chemistry System

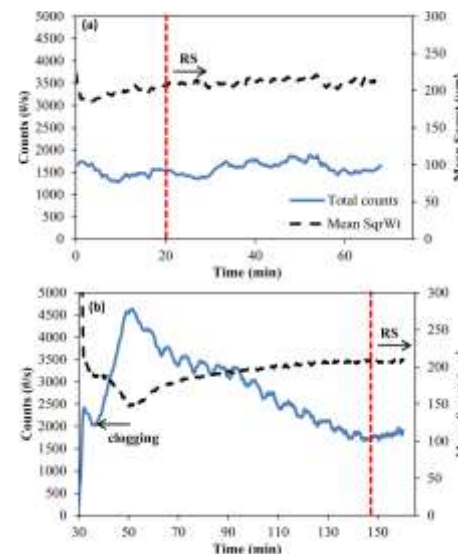
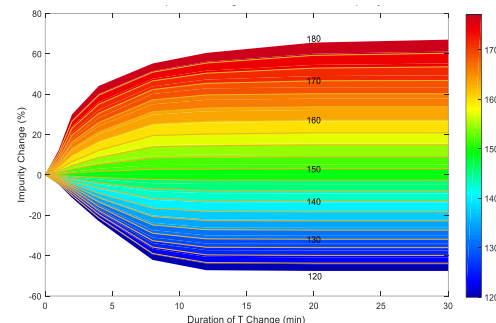


MSMPR System

Case Study #1: Continuous Manufacturing of APIs



- Developed PAT and model base approaches for monitoring product quality
 - Impact of a disturbance on product quality in general depends on the magnitude and the duration of the disturbance
- Investigated impact of process disruptions caused by clogging
 - Utilize product and process understanding to identify root cause
 - Demonstrate detectability of clogging events (e.g. pressure rise)
 - Establish performance criteria than can be tracked and used to drive continuous improvement



Research Outputs:
Developed PAT and models for in-process
monitoring of continuous API manufacturing

DOI: 10.1021/acs.oprd.7b00322
<https://doi.org/10.1016/j.compchemeng.2019.06.035>

FDA

A collage of images showing various pharmaceutical products. The top left shows a syringe and a small vial. The top center shows a blister pack of tablets. The top right shows a vial of liquid. The middle left shows a syringe with a red label. The middle center shows a vial of liquid. The bottom shows a row of small vials.

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Case Study #2: Quality Attributes of CCS for Parenterals

- Assessed two general categories of risks in pharmaceutical containers under normal storage and stress conditions
 - Mechanical stresses: breakage and crack
 - Chemical stresses: particulate generation, metal leaching etc.
- Applied orthogonal analytical methods to detect the extent of the failure mode and potential impact on product quality
 - freeze-thaw, lyophilization, compression, scratch tests; visual inspection, pH, particle size analyses, extractable, leachable and imaging studies



6 months 25°C		pH 3.7	WFI	pH 7.0	pH 10.0	pH 11.6
A	1					
	2					
	3					
	4					
	5					
	6					
	7					
B	1					
	2					
	3					
	4					
	5					
	6					
	7					
C	1					
	2					
	3					
	4					
	5					
	6					
	7					

Research Outputs:

Developed systematic platform testing approach capable of assessing common failure modes of pharmaceutical glass container closure systems

Challenge Question

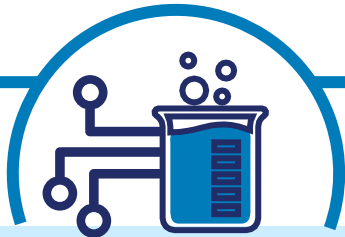


- Is this statement true or false?

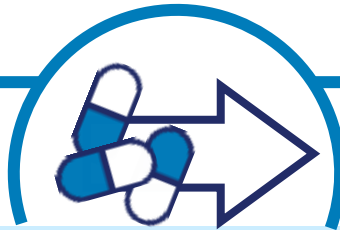
“FDA science and research activities and collaborations are crucial to informing Emerging Technology Team interactions with stakeholders”



Acknowledgements



OPQ
Collaborators



Emerging
Technology
Team



Industry

