FDA Research Supporting Emerging Technologies with Case Studies

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US FDA Center for Drug Evaluation and Research

CDER-SBIA Pharmaceutical Quality Symposium
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Learning Objectives

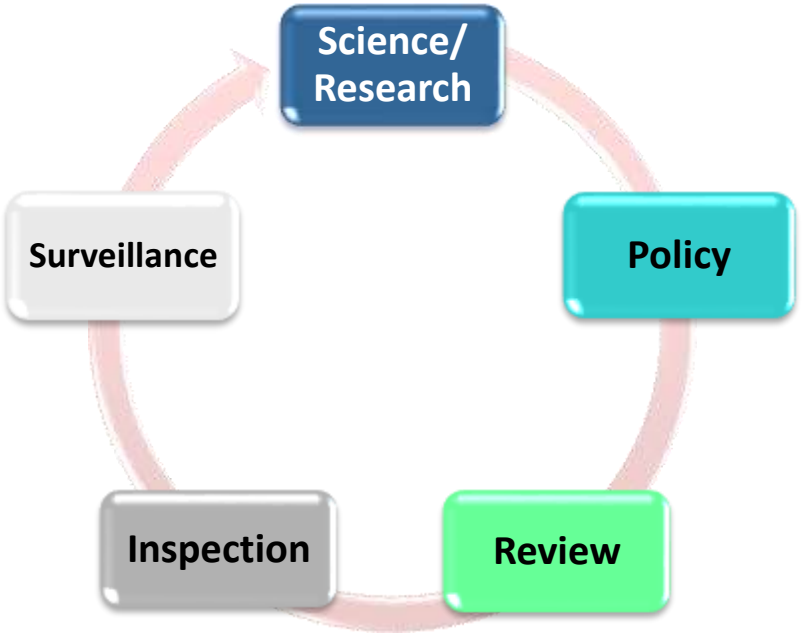
- Explain why research is needed to support CDER's Emerging Technology Program
- Describe how OPQ's research has impacted CDER's assessment of Emerging Technologies
- Locate opportunities to collaborate with the CDER to advance the scientific understanding of how emerging technologies impact pharmaceutical quality

Why is research needed for CDER in Pharmaceutical Quality?

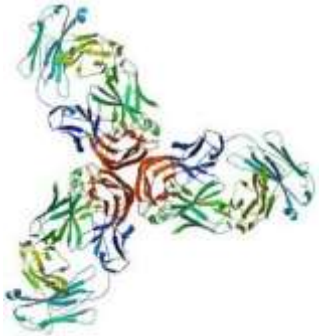
There is increased public awareness of importance for pharmaceutical quality.

Science and research are critical components for ensuring consistent product quality over the lifecycle.

- Pharmaceutical industry relies on the FDA to develop **guidance**, **standards and policies** for product quality to guide product development.
- Drug products and manufacturing processes are becoming more **complex**.
- OPQ provides alignment among all CDER functions and scientific approaches addressing drug quality for **both brand and generic drugs**.



OPQ Science and Research



1. *Manufacturing Science and Innovation*
2. Drug Quality Standards
3. *Advanced Characterization of Complex Mixtures and Biologics*
4. Physicochemical Characterization of Complex Dosage Forms and Formulations
5. Post-Market Product Quality and Public Health Issues
6. Immunogenicity and Immunology
7. Linking Biomarkers and Drug Attributes to Safety and Efficacy

New Drugs **Generic Drugs**

Biosimilars

Over-The-Counter **Biological Products**

A.C. Fisher, S.L. Lee, D.P. Harris, L. Buhse, S. Kozlowski, L. Yu, M. Kopcha, J. Woodcock. Advancing pharmaceutical quality: An overview of science and research in the U.S. FDA's Office of Pharmaceutical Quality. *Int. J. Pharm*. 2016.

Promoting OPQ Research Collaboration and Communication

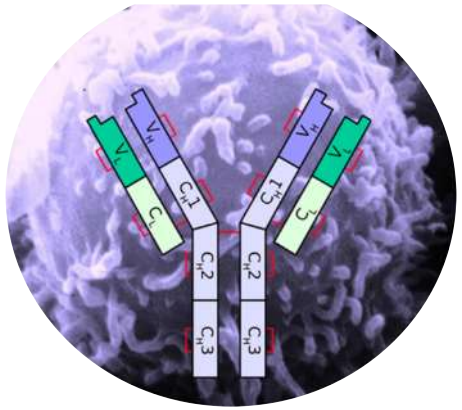
Centers of Excellence to facilitate productive research interactions, collaborations and communications

- OPQ established **Centers of Excellence (COE)** for Advancing Pharmaceutical Quality and Product Development in order to provide a **platform for scientific collaboration and communication**.
- Increased collaboration and communication will position CDER to more **efficiently respond to emergent issues, anticipate scientific needs, and engage and support the partners** of OPQ's scientific services in increasingly effective ways.

Contact OPQCOE@fda.hhs.gov

OPQ Centers of Excellence

Immunology

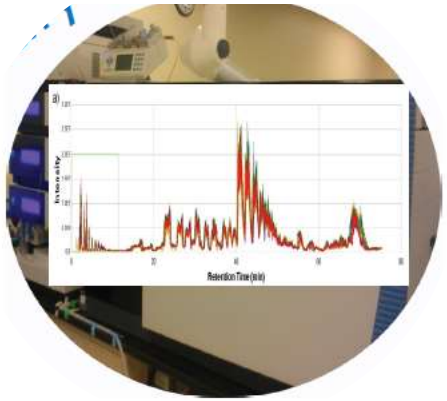


Manufacturing Science & Innovation

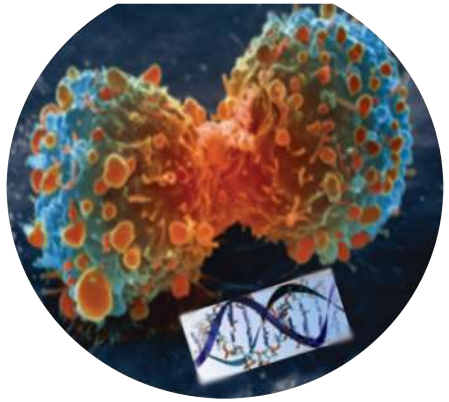
Manufacturing and Controls for Small Molecule Drugs

Manufacturing and Controls for Biological Products

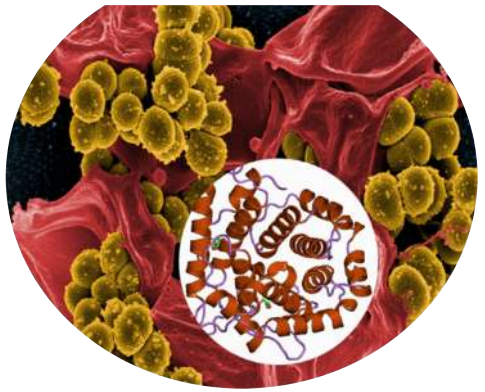
Pharmaceutical Analysis & Characterization



Tumor Biology

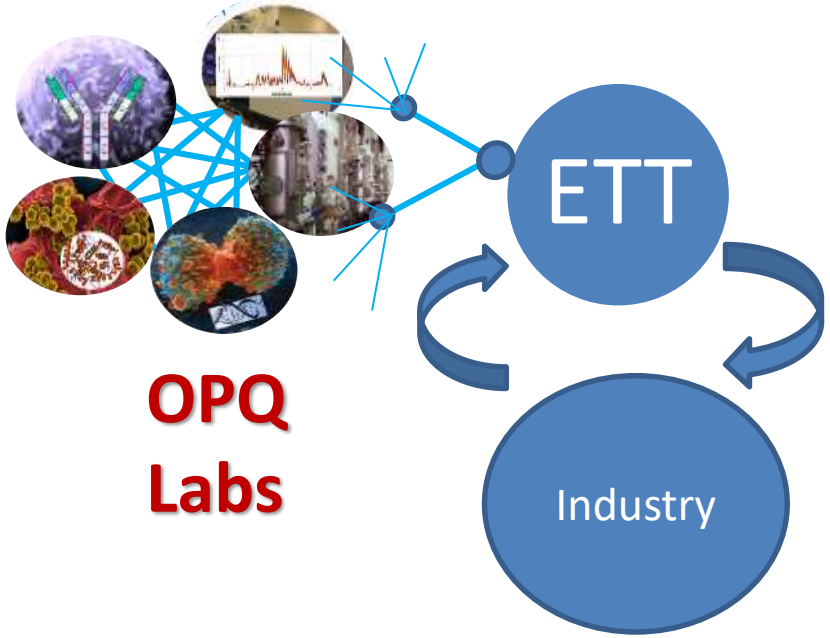


Infectious Disease & Inflammation



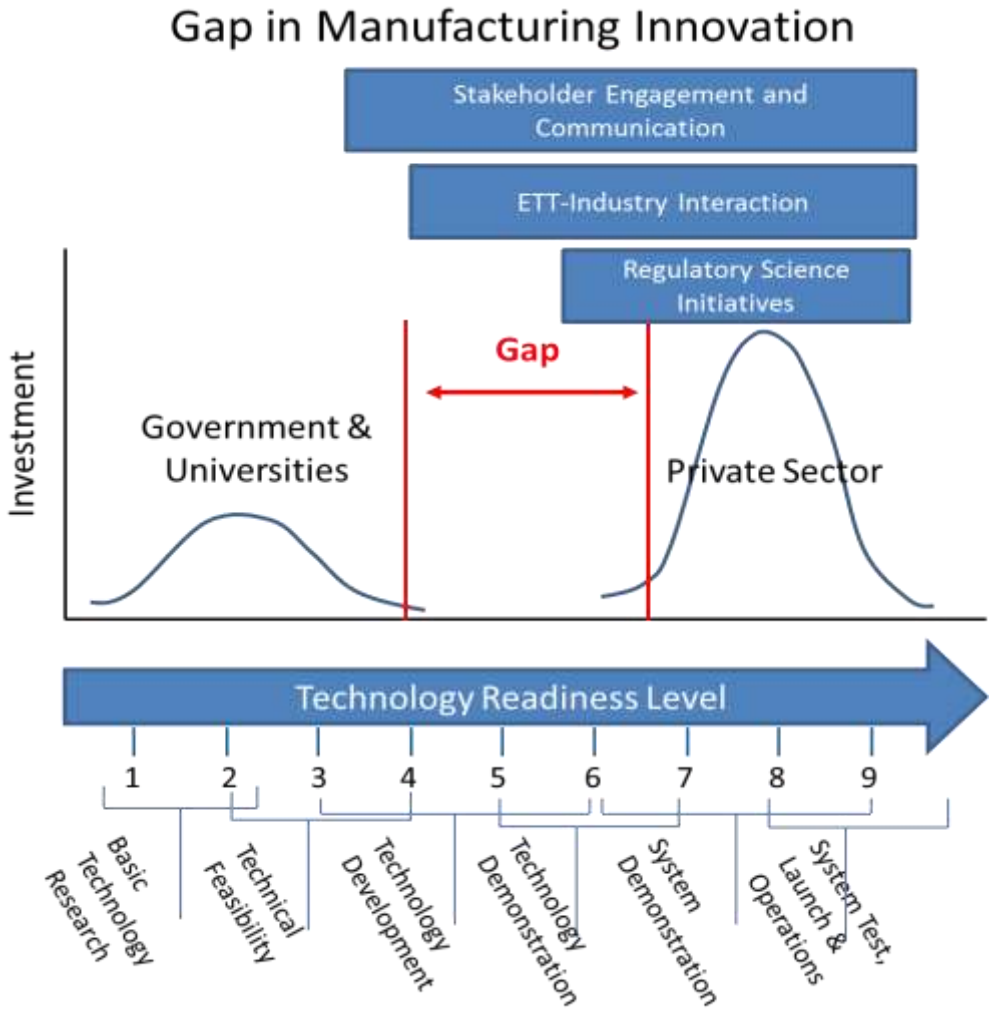
OPQ Research and Emerging Technology Program

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



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

Manufacturing Science and Innovation



- Many new manufacturing technologies fail to move from discovery to implementation and commercialization stages
- Emerging technologies in regulated industries may be subject to additional uncertainty in determining how the technology fits within existing regulatory approaches
- Collaborative research on the impact of emerging technologies on product quality can help to proactively address such regulatory uncertainties

O'Connor, T.F., et al. *International Journal of Pharmaceutics* 509 (2016): 492-498.

FDA Science and Research Activities: Emerging Technology

OPQ Lab 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

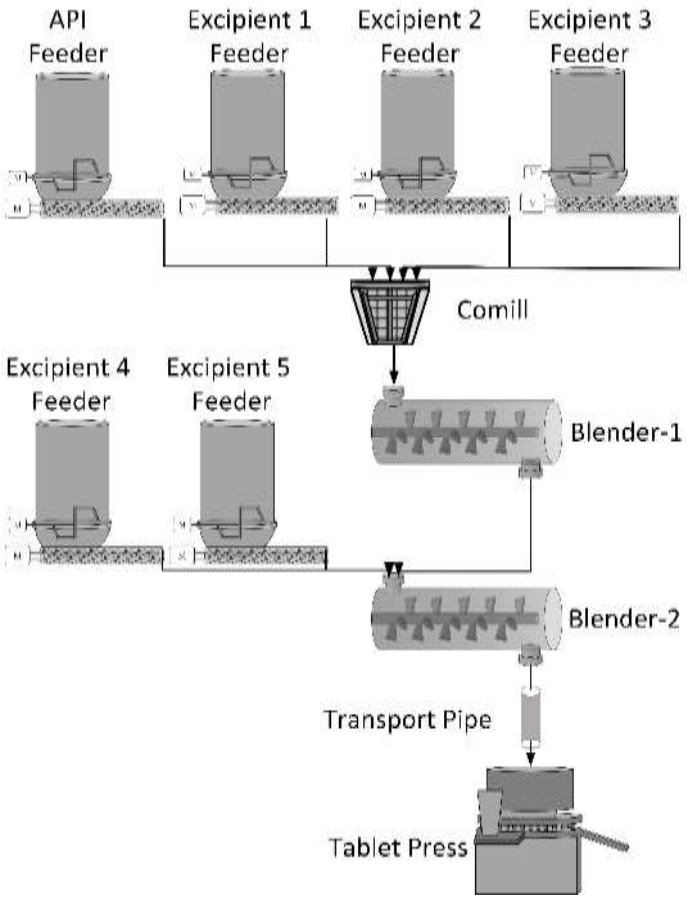
Emerging Therapies (oligonucleotides)

Case Studies

Case Study #1: Assessment of In-process control limits for Continuous Manufacturing

Question: Are the proposed operating limits to control material feeding acceptable for ensuring product quality?

- Process dynamics can be characterized by the Residence Time Distribution (RTD)
- Application of Residence time distribution (RTD) models
  - Predict blend and content variability based on feeding variability
  - Traceability and diversion of nonconforming material due to an unexpected even or disturbance
  - Support justification of excipient feeder limits

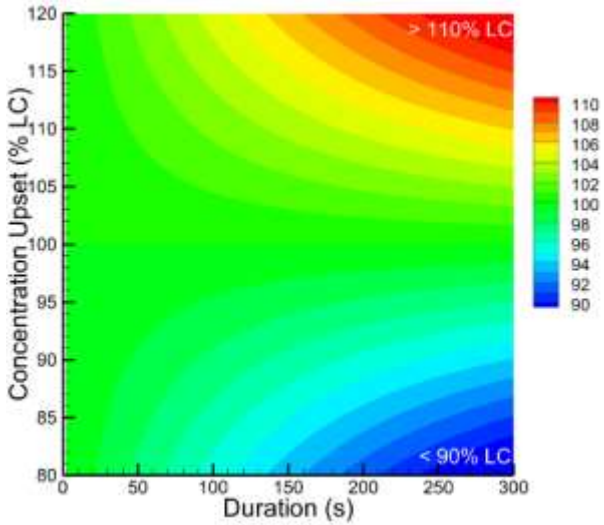


Example of Continuous Direct Process

https://doi.org/10.1016/j.compchemeng.2019.06.033

Case Study #1: Assessment of In-process control limits for Continuous Manufacturing

- OPQ research has developed process modeling and simulation tools to support the assessment of CM applications
  - Flowsheet models (i.e. integrated process models)
  - Post-processing tools that can facilitate risk assessments
- Collaborated with leading academic groups to develop process modeling and simulation tools



Credibility Factor	Activities
Code Verification	N/A
Calculation Verification	N/A
Governing equations	Sensitivity analysis performed on model form
Parameters	Sensitivity analysis performed on model parameters
Comparator	Comparators included different process conditions, API properties and formulation variation
Validation Assessment	Combination of visual and quantitative comparison of goodness of fit
Applicability	Validation covered ranges wider than proposed operating ranges

Research Outputs:

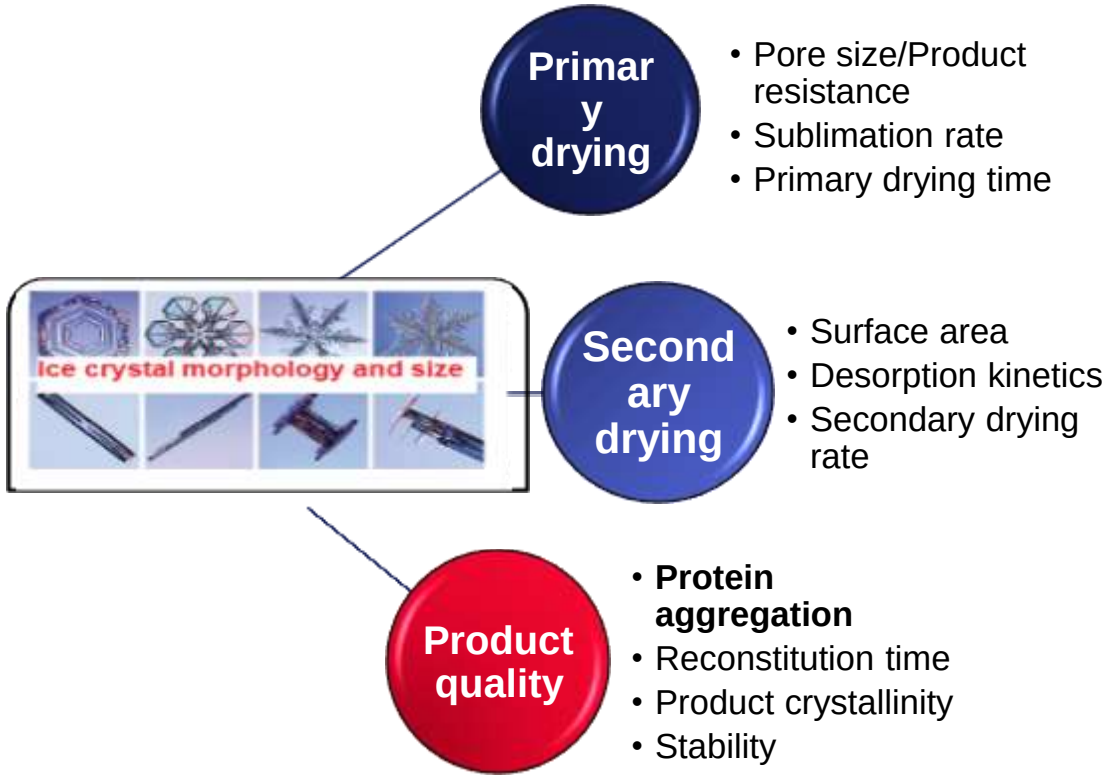
1. Modeling and simulation tools capable of assessing material feeding variability on product quality
2. Knowledge on assumptions and limitations of modeling tools – guide validation considerations

https://doi.org/10.1016/j.compchemeng.2019.06.033

Case Study #2: Lyophilization of Biological Products

Question: What are the considerations for detection and control of process deviations and possible product quality failure modes during novel lyophilization processes

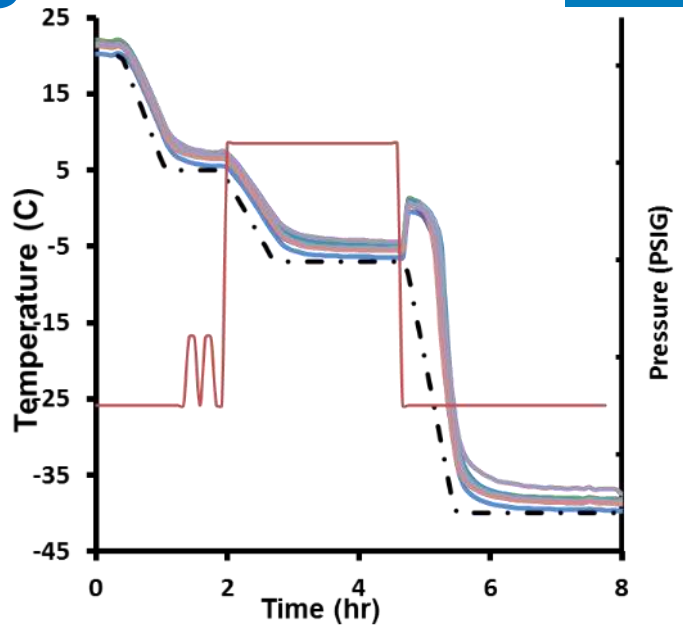
- Lyophilization most commonly used process for improving the stability of moisture labile pharmaceuticals, ~40% of biopharmaceuticals
- Controlled ice nucleation is based on pressurization and rapid depressurization of the drying chamber during the freezing step
- Nucleate simultaneously and therefore yield a product with low vial-to-vial variability, and uniform cake quality attributes

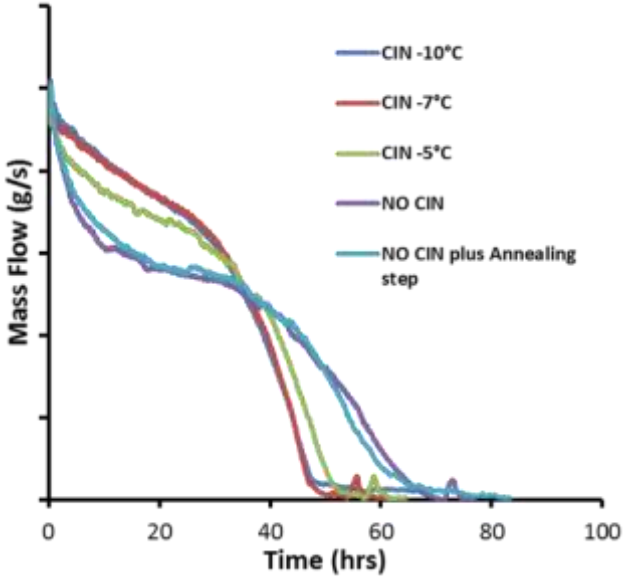


Case Study #2: Lyophilization of Biological Products

- OPQ research has developed a controlled-ice nucleation lyophilization manufacturing platform
- Implementation and validation of PAT tools for controlling the process and monitoring product quality
- Compare product quality, in-use and storage stability of different modalities of biologics lyophilized with different freezing techniques

Research Outputs:
Developed a risk map linking CIN process parameters to product quality attributes





Case Study #3: Quality Attributes of CCS for Parenterals

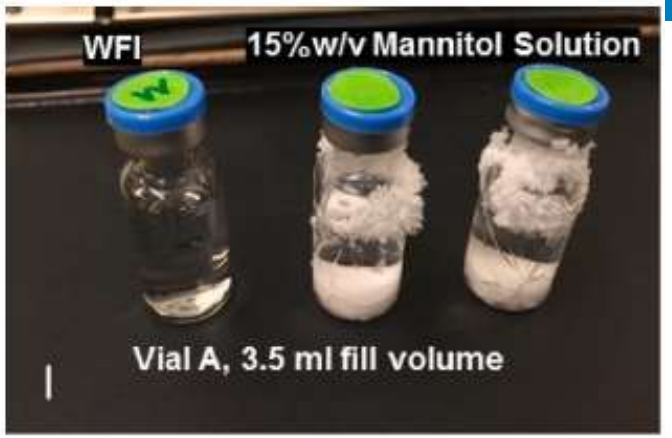
Question: What is the assessment of the current state of pharmaceutical quality of parenteral container closure systems

- There have been recalls due to glass flakes, breakage, and/or particles observed in marketed formulations,
  - E.g. epoetin alpha injection, sodium thiosulfate injection, and amikacin sulfate injection
- Borosilicate glass vials may undergo dissolution of glass network at high pH or at elevated temperatures
- Other common problems observed in glass containers are breakage, cracks, chipping, and particulate generation due to stresses encountered during drug product manufacturing transportation or during administration

Case Study #3: 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

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



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						

Srinivasan C. *et. al.* Int. J. Pharma. 568 (2019) 118510

External Collaboration Opportunities

OPQ Research Collaborations

- Collaborations allow OPQ to leverage external expertise and capabilities to address regulatory science topics
- Cooperative Grants
  - Advancing Manufacturing Processing and Control Strategies for Drug Substances and Drug Products
  - Enhancing Regulatory Science for the Risk Based Assessment of Emerging Manufacturing Technologies
- FDA Broad Agency Announcement
  - Topic Area 3: Support New Approaches to Improve Product Manufacturing and Quality

Manufacturing Research Collaboration

Collaborations via grants and contracts

Industry 4.0 Implementation in Continuous Pharmaceutical Manufacturing (Rutgers/Purdue)

Feeding, Blending, Direct Compression (Rutgers/Purdue)

Smart Data Analytics for Risk Based Regulatory Science and Bioprocessing Decisions (MIT)

Synthesis, Crystallization, and Isolation of an API: Process Model-Controlled Enzymatic Synthesis of Beta-Lactam Antibiotics (Georgia Institute of Technology)

End-to-End Continuous Manufacturing (Continuus)

Downstream Bioprocessing (Chromatan)

Continuous Bio-purification (Chromatan)

Continuous Direct Compression (Rutgers)

Challenge Question

- Is this statement true or false?

"Research conducted by OPQ's COEs have directly impacted the assessment of submissions to the Emerging Technology Program"

- This is **TRUE**.
- OPQ also utilizes collaborations to leverage external expertise and capabilities to address regulatory science topics

Acknowledgements

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