FDA's Advanced Manufacturing Product Development Science Program

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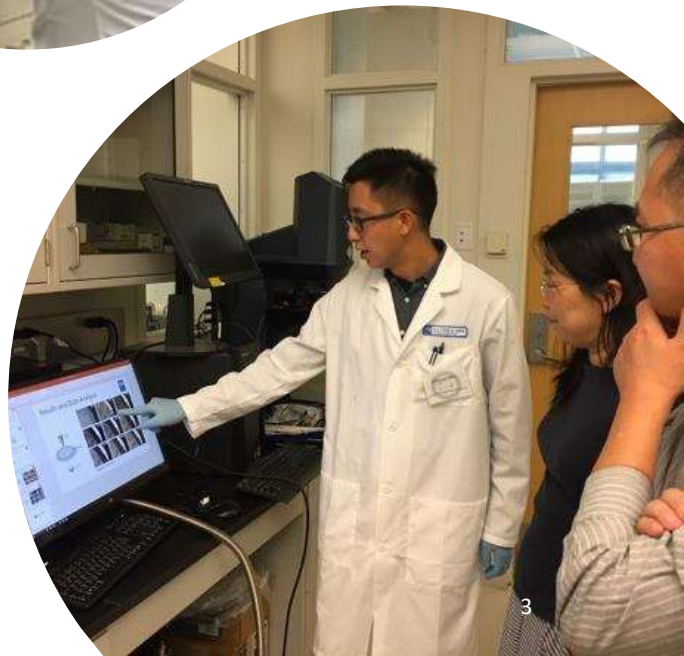
Learning Objectives

- Describe OPQ's advanced manufacturing product development science capabilities
- List current advanced manufacturing product development focus areas
- Explain the impact of product development science on OPQ's mission

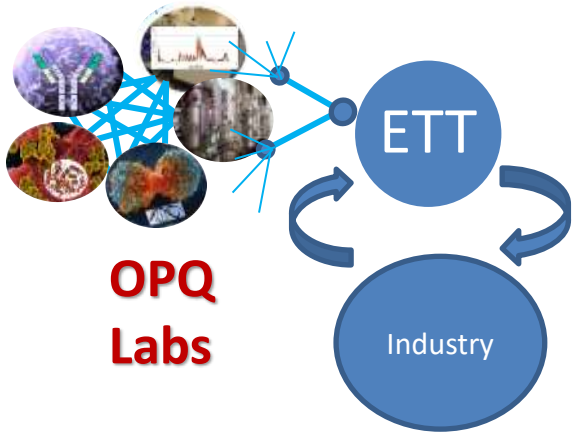
OPQ Science and Research

- **Enhance** the FDA's capacity for evaluating and monitoring drug quality, safety, and efficacy
- **Modernize** current regulatory pathways or **indicate** a new regulatory pathway where there is currently none
- **Address** regulatory and scientific issues that are mission critical
- **Maintain** a state of *science and research readiness* that anticipates potential regulatory needs while allowing for rapid response to emergent regulatory issues



OPQ Research and Emerging Technology Program

- Knowledge gained from the internal and sponsored research inform policy, review, inspection, and surveillance activities
- Ensure 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

OPQ Product Development Science Capabilities

Novel manufacturing methods

- Continuous manufacturing, 3D printing

Precision analytics

- HRMS, NMR

Process analytical technology

- NIR, Raman, imaging, advanced process control

Modeling and Quantitative Analysis

- Physics-based modeling, multivariate analysis, machine learning

Complex products

- Extrusion, Emerging therapies (oligonucleotides)

Continuous perfusion bioreactor

3D Printing

High resolution mass spectrometry

Product Development Science Program

Intramural Research
Novel Manufacturing Methods (10 projects)
Precision Analytics (16 projects)
Advanced Manufacturing of Biopharmaceuticals (11 projects)
Manufacturing of Glycoproteins (3 projects)
Manufacturing of Synthetic Nucleic Acid Sequences (1 project)
Process Modeling, and Artificial Intelligence (AI)/ Machine Learning (ML) (4 projects)

Projects generated more than 65 internal reports and publications

Product Development Science Program - Extramural

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

- Multiple mechanisms to sponsor collaborations
  - OPQ U01 grants
  - FDA Regulatory Science Broad Agency Announcement

Continuous manufacturing of lipid nanoparticles (UConn)

End to End continuous manufacturing (Continuus)

Continuous bio-purification (Chromatan)

Continuous direct compression (Rutgers)

Product Development Science Program

Extramural collaborations via grants and contracts
Industry 4.0 and Smart Manufacturing (3 projects)
Novel Manufacturing Methods (6 projects)
Novel Process Analytical Technologies (4 projects)
Process Modeling and Simulation (2 projects)
Advanced Manufacturing Training (1 project)

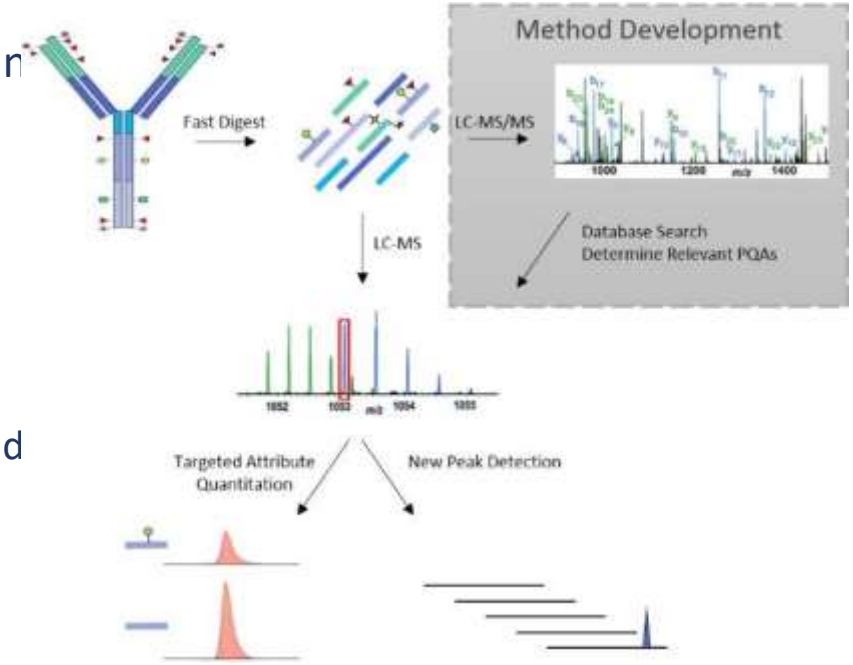
Projects generated more than 13 publications

Examples

Precision Analytics

Multi-Attribute Method (MAM)

- MAM: LC-MS based peptide mapping method proposed for control testing of therapeutic protein
- Points to consider for implementation:
  - Risk assessment
  - Method validation
  - Capabilities and specificities of new peak detection feature
  - Comparison to conventional methods
- Established in-house MAM capabilities
  - Method validation, new peak detection analysis, and comparisons with conventional methods
- MAM research has aided in evaluation and understanding of ETT MAM applications
  - Multiple applicants at different stages of product development
  - Agreed to sunset strategy for conventional methods for one applicant



Rogstad, S. et al., Analytical Chemistry, 2019.

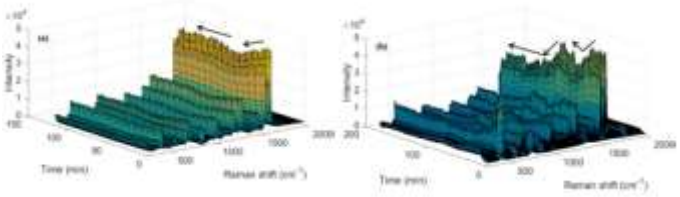
Examples

Novel Manufacturing Methods

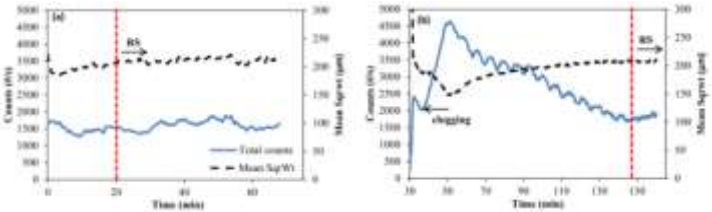
Continuous Synthetic API Manufacturing

- Growing industry adoption
- Major points to consider for implementation
  - Impact on impurity profile
  - Process monitoring and control
- Established intramural and extramural collaborations for flow synthesis and crystallization
  - Process design to minimize product quality risks
  - Development and validation of PAT methods
  - End-to-end manufacturing (Continuus)
- Support application assessment and ETT feedback
- Support development of ICH Q13

Raman Spectroscopy: Measure CBZ concentration and form



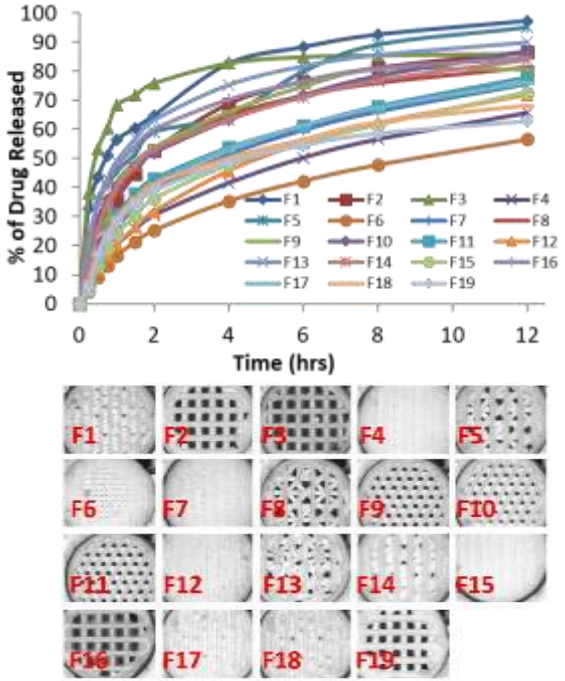
FBRM: Chord length distributions (CLD); monitor steady state and any disturbances



Testa, C. J., et al. (2020). Organic Process Research & Development 24(12): 2874-2889
Acevedo, D., et al. (2018). Organic Process Research & Development 22(2): 156-165

3D Printing of Drugs

- Opportunity for precision medicine
- Major points to consider for implementation
  - Material selection
  - Impact of design on CQAs
- FDA shared facility for 3D printing
  - Characterization on intermediate products
  - Prediction of CQAs
  - Design of complex products (e.g., polypills)
- Support pre-application ETT feedback for multiple sponsors



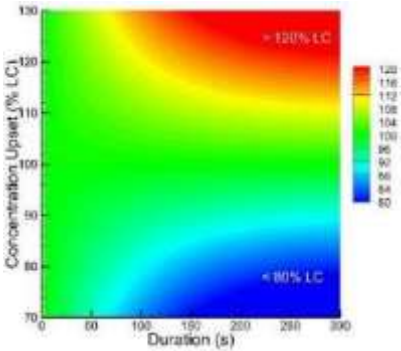
Zidan, A. *et. al.,* Int J Pharm. 2019 Jan 30;555:109
Zidan, A. *et. al.,* Int J Pharm. 2019 Jan 10;554:292

Examples

Process Modeling and Quantitative Analysis

Residence Time Distribution Modeling

- Growing utilization of RTD process models to support control strategies for continuous manufacturing
  - Material traceability
  - In-process control for monitoring product CQAs
- Major points to consider for implementation
  - Impact of method parameters on RTD characterization
  - Impact of material properties and process parameters on model predictions
  - Risk based validation
  - Considerations for lifecycle maintenance
- Established intramural and extramural collaborations using round robin approach for model validation
- Regulatory impact of process modeling research results
  - Support application assessment of RTD models and ETT feedback
  - Provide training simulations for internal CM reviewer training



Funnel plot from RTD model predicting impact of disturbance on product quality

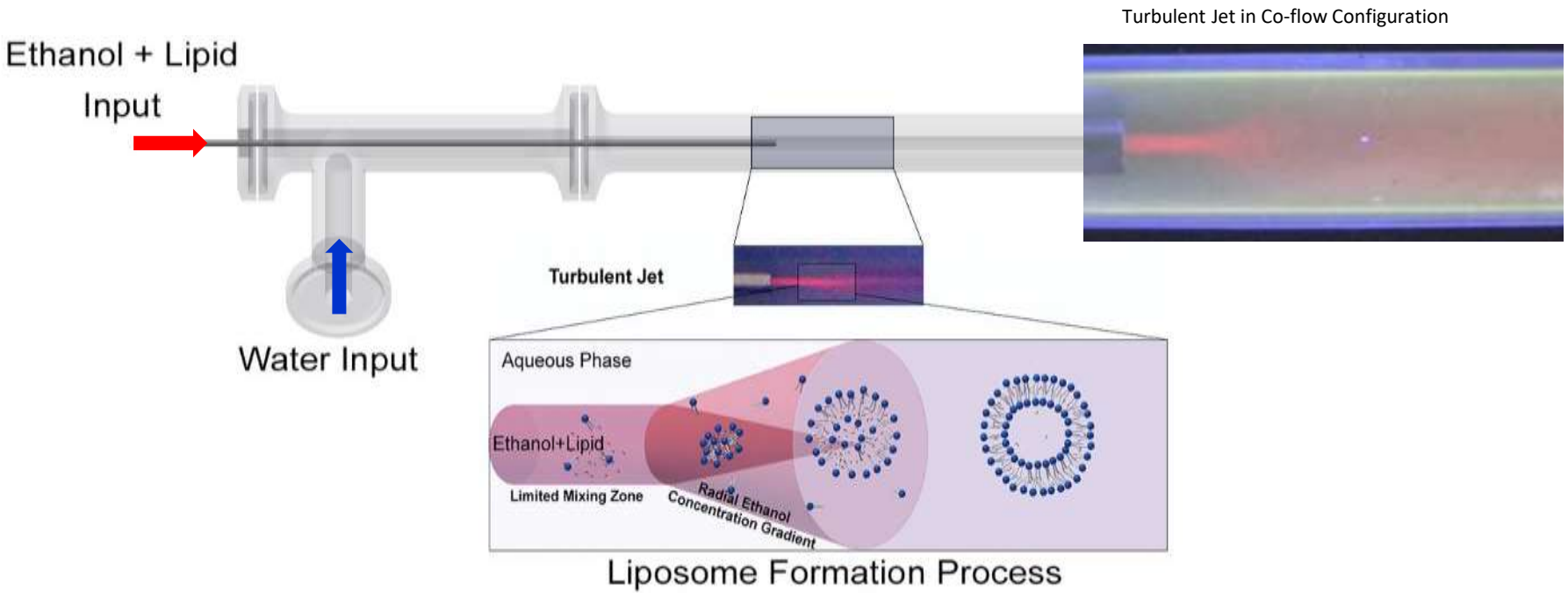
Tian, G. *et. al.* Comp. & Chem. Eng. 2019
Tian, G., *et al.* (2021). Aaps Pharmscitech

Examples

Complex Product Design

Continuous Manufacturing: One-step Unilamellar Liposome Formation

Collaboration with University of Connecticut (PI: Prof. Diane Burgess)

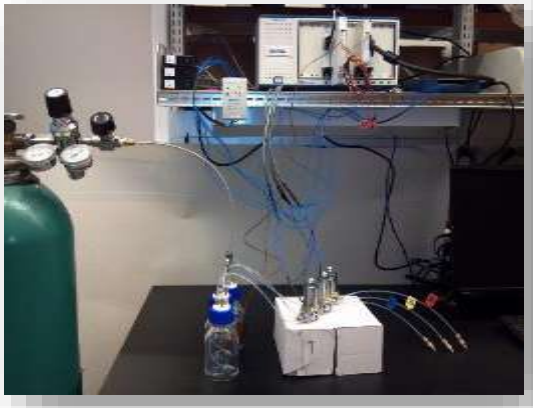


A. Costa, et al. Liposome formation using a coaxial turbulent jet in co-flow. Pharm Res. 2016, 33(4):404-416

Continuous Manufacturing of Nanoparticles

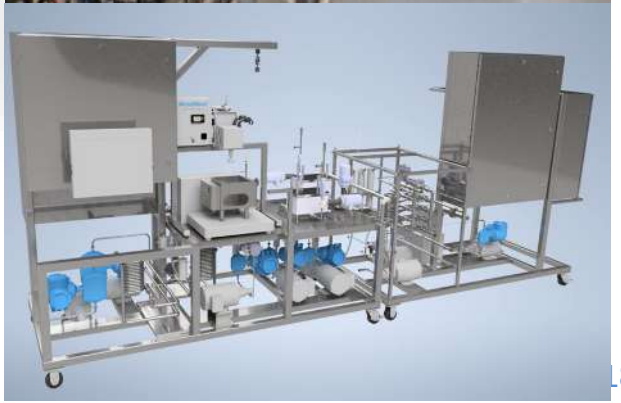
Images from early concept to final system
(Slide courtesy of Diane Burgess and Antonio Costa)

2014



2018

2021



Benefit of Continuous Manufacturing:

- Reduction in processing time per unit dose.
- Reduction in equipment footprint requirements.
- Potential flexibility in duration of manufacturing campaigns based on knowledge of process.
- Rapid response to drug shortages, emergencies, patient demand

Funding: HHSF223201310117C, HHSF223201610121C, and 1U01FD005773-01

Summary of Outcomes and Impact

- Directly supported ETT feedback and application assessment for over 10 ETT projects
- Policy and guidance development
  - Informed development of ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products
  - Supporting development and implementation for FRAME
- Workforce development
  - Provided training to support ETT graduation of continuous direct compression

Future Directions

- CDER Research Manufacturing Pilot Plant
  - Increase FDA's capability to generate knowledge and train FDA staff
- Continued investment in research programs for growing area in advanced manufacturing
  - Awarded five new collaborative projects in Sept. 2021
- Continued alignment of research programs to support ETP and development and implementation of FRAME

Summary

- OPQ has developed product development science capabilities across several key areas in advanced manufacturing
- Leveraging external collaborations to enhance OPQ's capabilities
- Product development science programs are aligned to address mission relevant regulatory and scientific issues
- Product development science program have supported assessment, inspection, and policy and guidance development for advanced manufacturing

Challenge Question #1

Identify product development science focus area for advanced manufacturing:

A. Continuous Manufacturing

B. Precision Analytics

C. Process Modeling

D. All of the Above

Challenge Question #2

Which of the following statements is NOT true?

A. Product development science program only involves internal FDA research

B. Product development science program is aligned with the implementation needs of FRAME

C. Product development science program has impacted quality assessment, policy development, and workforce training

D. CDER research manufacturing pilot plant will increase FDA's capability to generate knowledge and train FDA staff

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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