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Innovation and Regulatory Landscape: Emerging Technologies Program

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Disclaimer

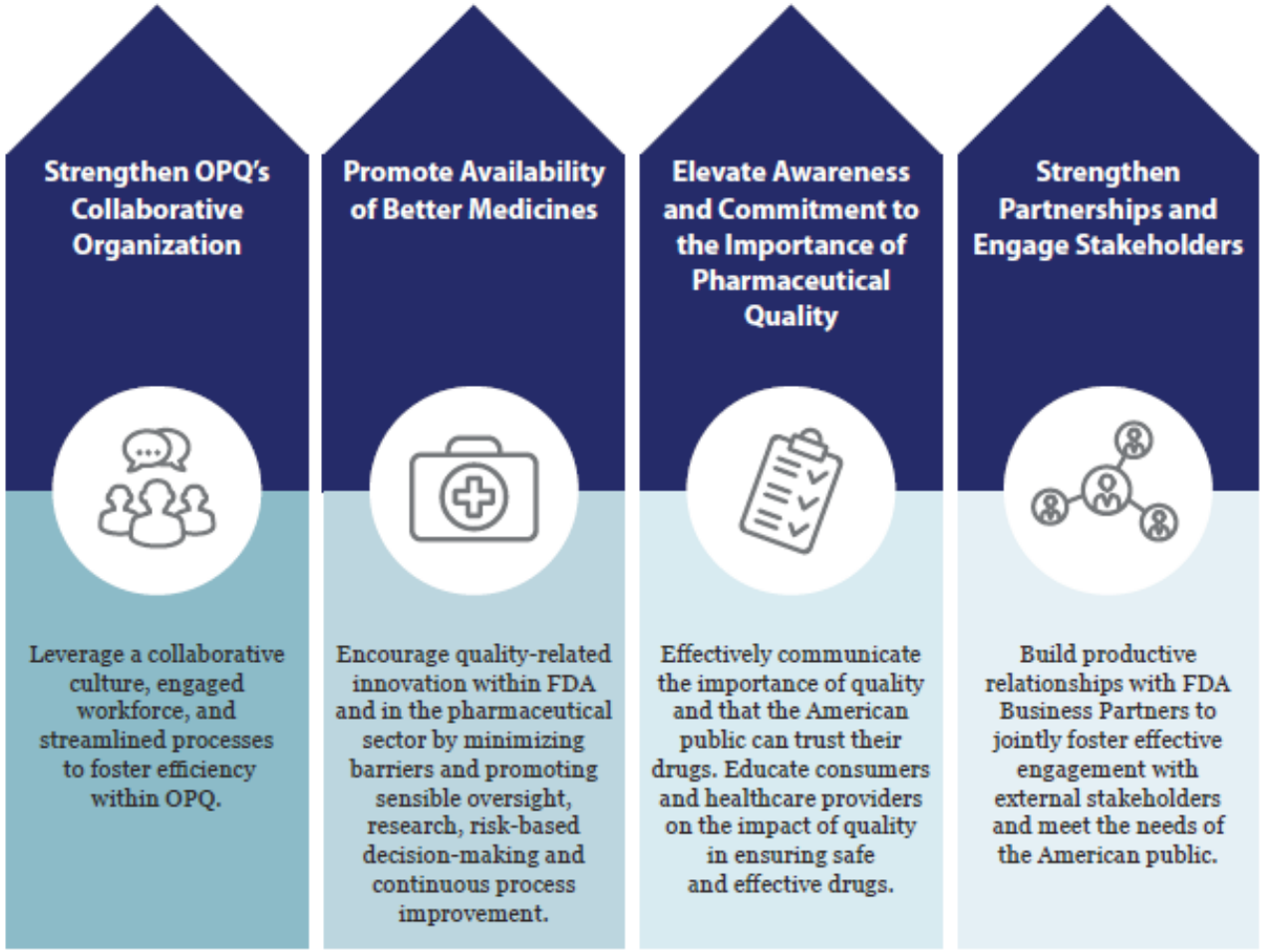
This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies

The Desired State

The Vision

"A maximally **efficient**, **agile**, **flexible** pharmaceutical manufacturing sector that **reliably produces high quality drugs** without extensive regulatory oversight."

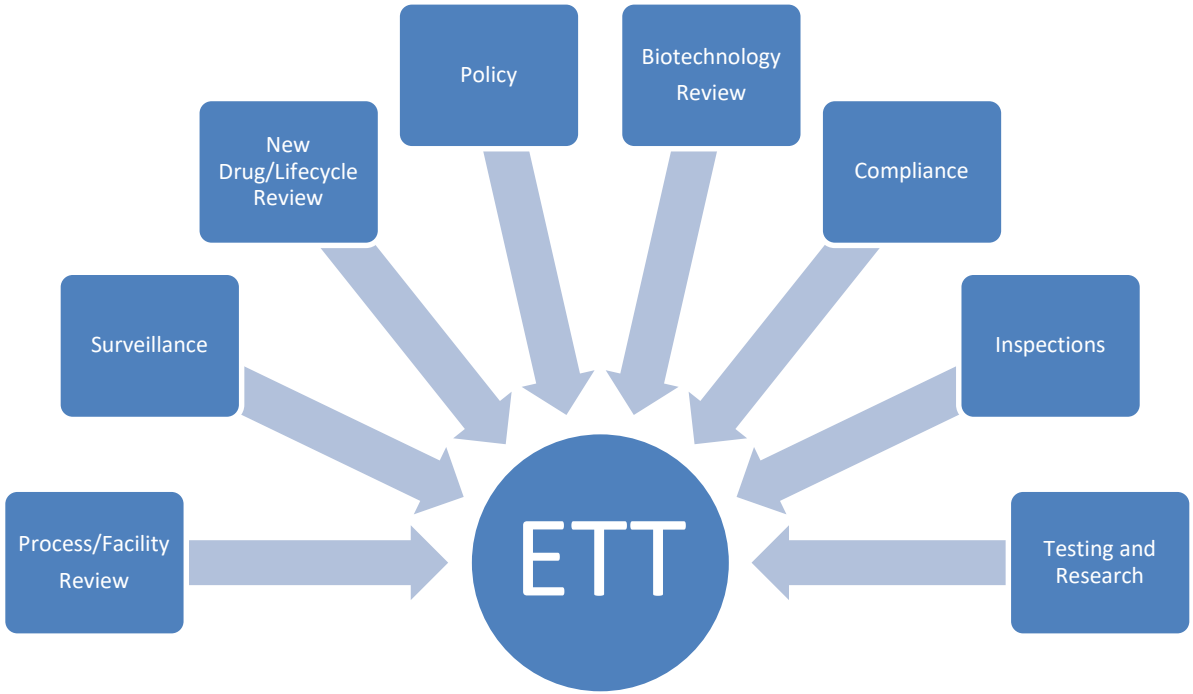
CDER's Office of Pharmaceutical Quality Strategic Priorities



Encouraging innovation in pharmaceutical sector is an OPQ strategic priority

Emerging Technology Team

Vision: 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** review and inspection programs (OPQ/CDER & ORA)

Comprehensive Approach under the Emerging Technology Program

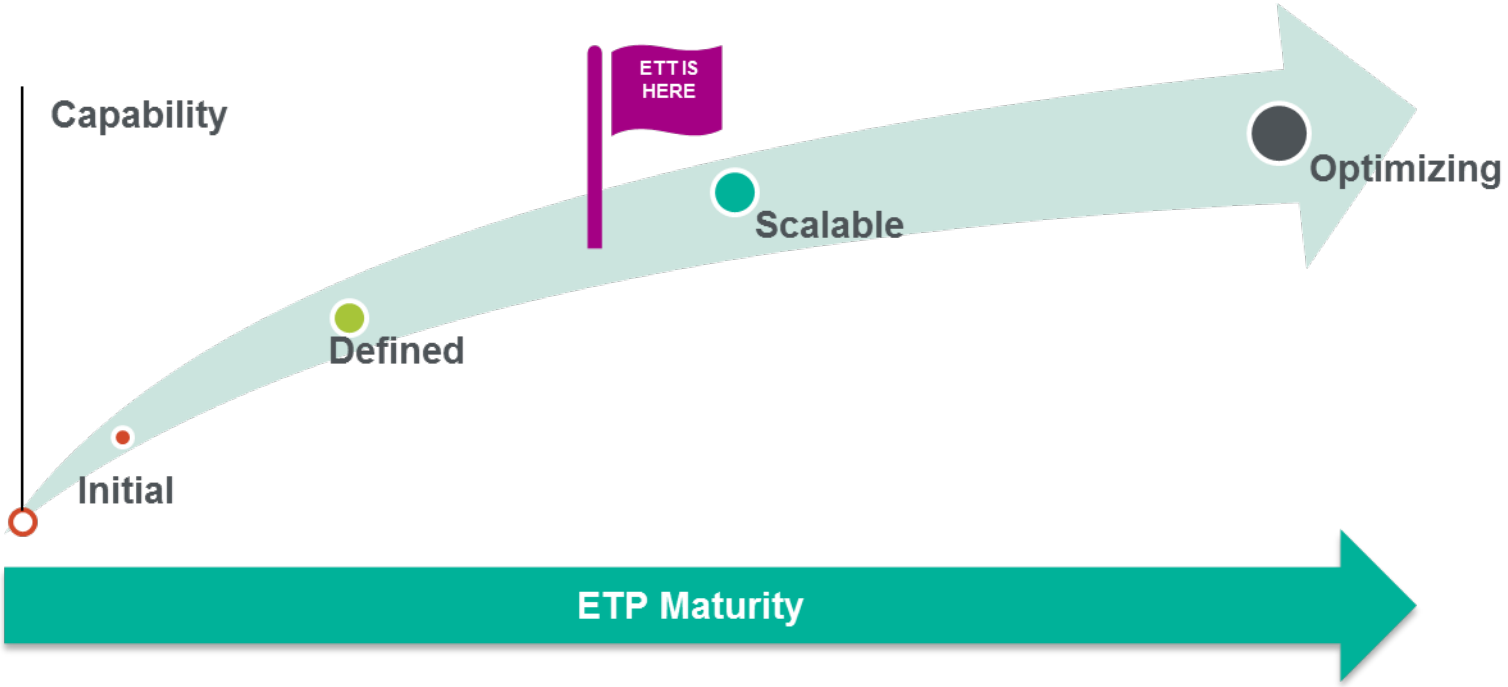
- **Early Engagement (Pre-submission)**
  - Face-to-face meeting(s) with ETT involvement – provided upfront scientific input under the Emerging Technology Program
- **Emerging Technology Site Visit if needed**
  - Participation by OPQ (including the ETT member(s)) and/or ORA members
- **Integrated Quality Assessment (IQA)**
  - Interdisciplinary team with experts in Drug Substance, Drug product, Process/Facility, Biopharm, and/or Inspection
  - ETT member as an Application Technical Lead (ATL) or co-ATL to lead the IQA team when the ET impacts most part of a CMC section
- **Pre-Approval Inspection (PAI)**
  - Conducted by team members from OPQ (including the ETT Member(s)) and ORA.

1. **The same ETT representative(s) will be involved in the entire process**
2. **The composition of a review team will likely remain the same throughout the entire process**

Emerging Technology Program Progress

- More than 30 requests accepted to the CDER Emerging Technology Program since the launch of the program in late 2014
  - A total of 60 ETT-industry interactions (including both t-con and face-to-face meetings) since multiple interactions were held for some of the 32 requests
- Emerging Technology Guidance Finalized
- Emerging Technology Program Website

ETT Program Maturity



Maturity Roadmap

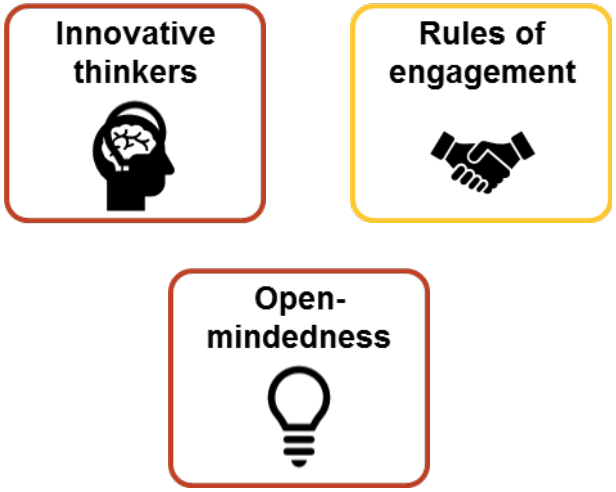
Developing | Emerging | Strategic | Global-Influencing

Emerging Technology Program: Industry Feedback

We solicited feedback from past and current program participants across three categories: **Value, Process, and Awareness**

Average overall satisfaction rating:

8.9/10



Value

ETT's open-mindedness and cross-office representation demonstrates commitment to encouraging innovation

Spreading collaborative and open-mindedness culture to other review channels could increase impact

Process

Industry derives value from ETT's collaborative approach and transparency throughout all project phases

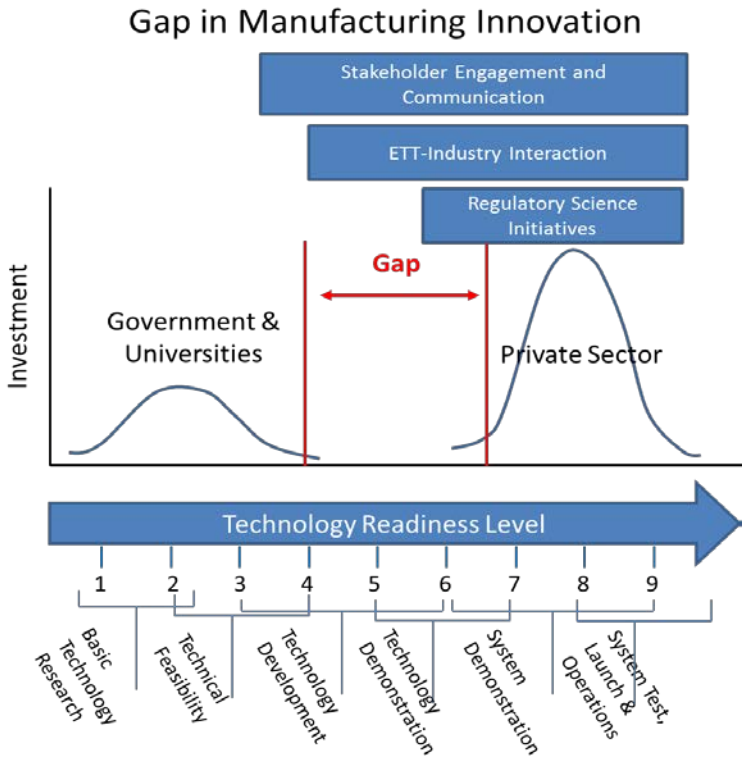
Inconsistency with timing makes processes seem opaque, even though they are compliant with Type C meeting guidelines.

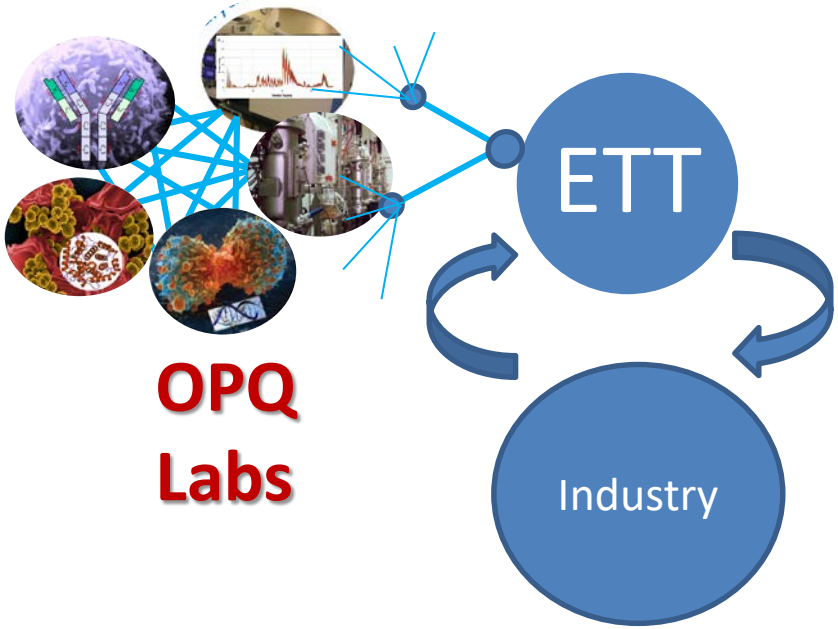
Awareness

ETT has gained relevance, visibility, and a positive reputation across the industry.

FDA Science and Research Activities on Emerging Technologies

- OPQ Science and Research
  - 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

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

FDA Experience: Emerging Technologies

- Emerging technologies for small molecules
  - **Continuous manufacturing of drug substance/product**
  - **Model-based control strategy for CM**
  - 3D printing manufacturing
  - Ultra long-acting oral formulation
- Emerging technologies for biological molecules
  - **Continuous manufacturing of biotechnology products**
  - Controlled ice nucleation for lyophilization processes
  - **Advanced process control: predictive modeling**
  - Comprehensive product testing using a single multi-attribute assay (multi-attribute method)
  - Next generation sequencing
- Emerging technologies for multiple products
  - Closed aseptic filling system
  - **Novel CCS for injectable products**

Emerging Technologies Progress: External Grants and Contracts

Emerging Technology Program and 21st Century Cures: FY2018
https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm615431.htm

- Rutgers University (Piscataway, N.J.), Industry 4.0 Implementation in Continuous Pharmaceutical Manufacturing
- The Massachusetts Institute of Technology (Cambridge, M.A.), Smart Data Analytics for Risk Based Regulatory Science and Bioprocessing Decisions
- Georgia Institute of Technology (Atlanta, G.A.), Continuous Synthesis, Crystallization, and Isolation (CSCI) of an API: Process Model-Controlled Enzymatic Synthesis of Beta-Lactam Antibiotics

ETT Science and Research Activities: Continuous Crystallization

Multi-stage mixed product removal (MSMPR) system

- Process dynamics studies (RTD and disturbance)
- Validation of PAT methods for state of control and CQA in process control
- Understanding of encrustration risks
- Population balance model for cooling crystallization

Oscillatory Baffle Crystallizer

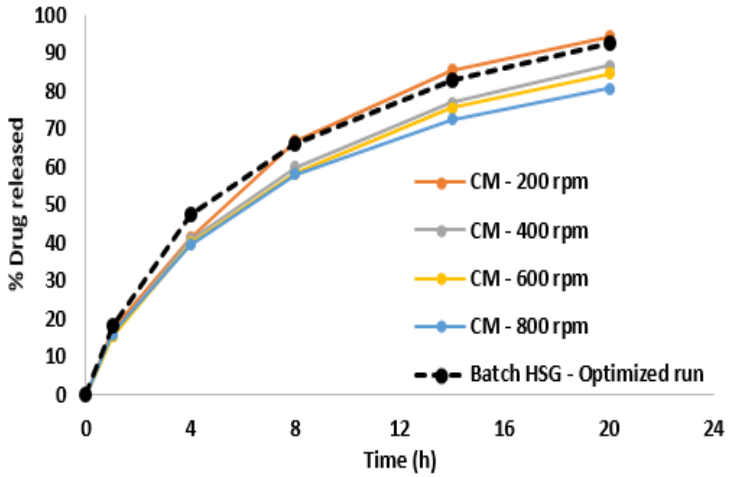
- Installation and qualification, unseeded runs, residence time characterization

Risk Considerations on Developing a Continuous Crystallization System for Carbamazepine
Xiaochuan Yang, David Acevedo, Adil Mohammad, Naresh Pavurala, Huiquan Wu, Alex L. Brayton, Ryan A. Shaw, Mark J. Goldman, Fan He, Shuaili Li, Robert J. Fisher, Thomas F. O'Connor, and Celia N. Cruz
Organic Process Research & Development **2017** *21* (7), 1021-1033
DOI: 10.1021/acs.oprd.7b00130

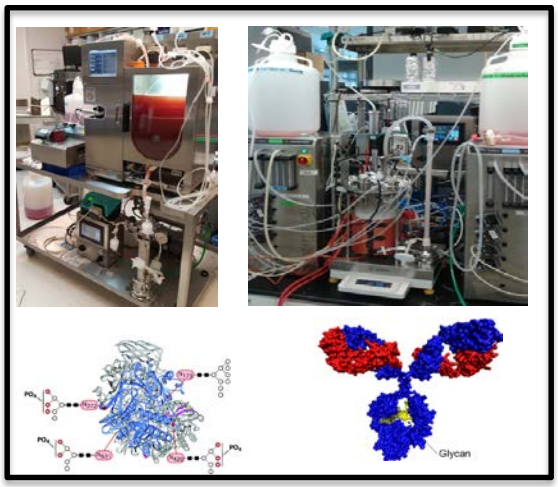
Raman Spectroscopy for Monitoring the Continuous Crystallization of Carbamazepine
David Acevedo, Xiaochuan Yang, Adil Mohammad, Naresh Pavurala, Wei-Lee Wu, Thomas F. O'Connor, Zoltan K. Nagy, and Celia N. Cruz
Organic Process Research & Development **2018** *22* (2), 156-165
DOI: 10.1021/acs.oprd.7b00322

Continuous Manufacturing

- Standards (e.g. USP, ASTM) and regulatory guidance (FDA draft guidance, ICH Q13 Working Group) for CM are being formulated
- Application of the technology to a wider range of products, including complex products, continues to grow
- Process monitoring approach is a common ETT-Industry discussion are for CM
  - Enables high detectability of transient disturbances and other key elements of control strategy such as active process control, material diversion and real time release testing (RTRT)
  - Process monitoring approach should consider: Variables being monitored; Sampling plan and relationship to process dynamics; and Data analysis
- Observability of product attributes in real-time can be more challenging for complex products



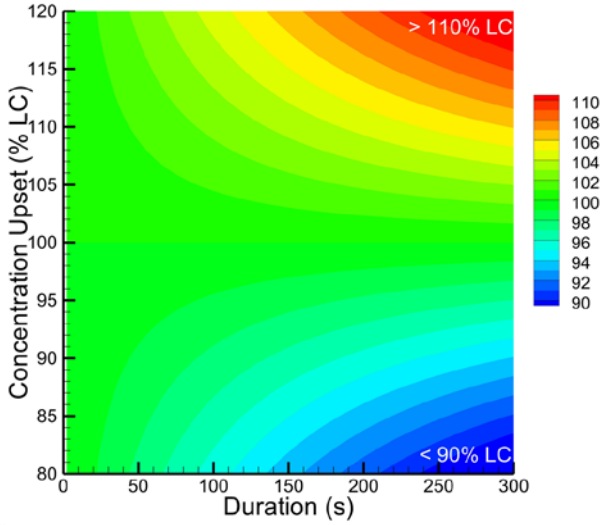
Modified release product produced via continuous wet granulation

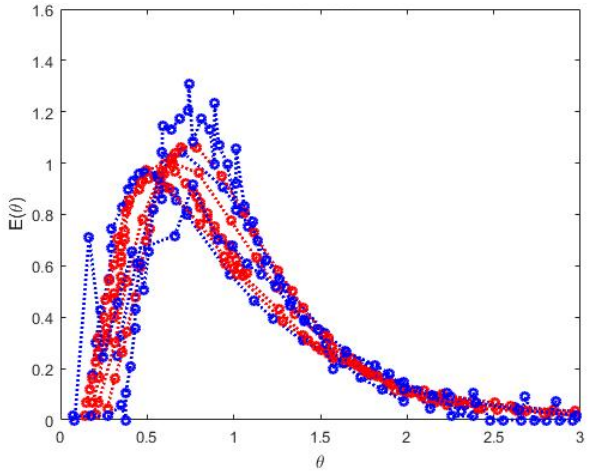


Continuous perfusion bioreactors

ETT Science and Research Activities: Application of Modeling for QRM

- 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
- Understand risks to validity of model predictions
  - Understanding process dynamics in relation to material properties, equipment design, and process conditions
  - Model parameter uncertainty
  - Expected variation in process parameters and material attributes *including line rate*
- Developing statistical approaches to compare RTD
  - Evaluate changes over the process lifecycle

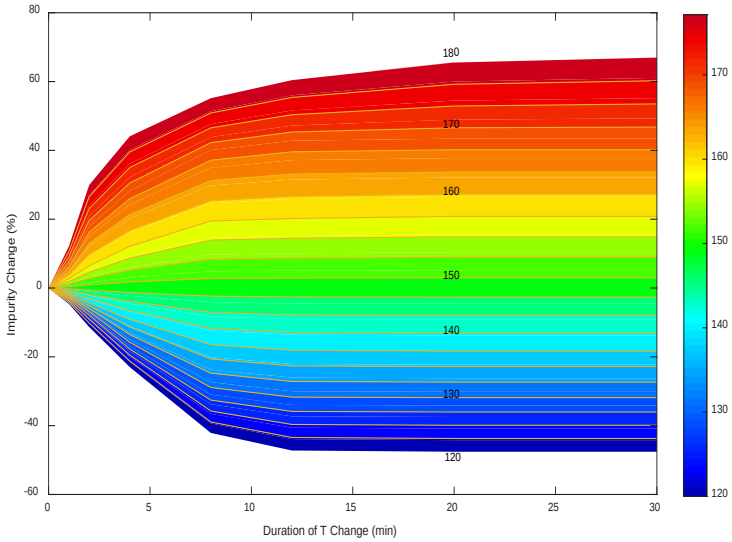




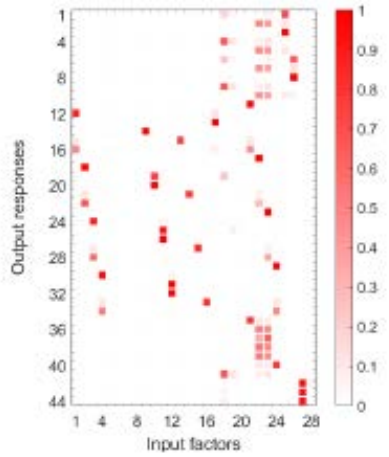
Tian G., et al. *Powder Tech.* 315 (2017): 332-338.

Process Modeling, Simulation and Advanced Control

- Increasing role of models in the CM control strategy
  - Models can be used as in process control if they:
    - Consider all relevant factors and their variations
    - Reflect commercial operating conditions
    - Show adequate predictive power for the intended purpose through proper validation
- Investigating assumption and limitation of different modeling approaches
- Exploring utility of a risk informed model credibility assessment framework (ASME V&V 40)
- At the FDA, increasing role of models in the quality assessment of CM applications



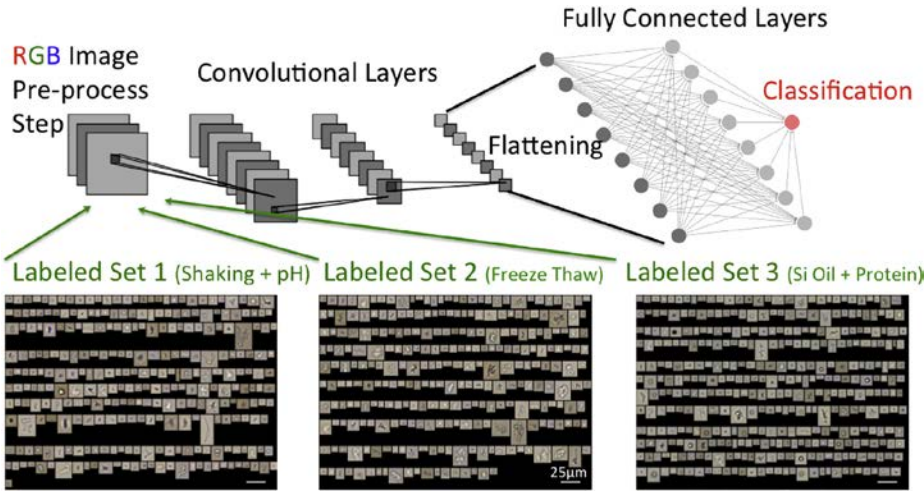
Change in Impurity Formation due to Temperature Disturbance



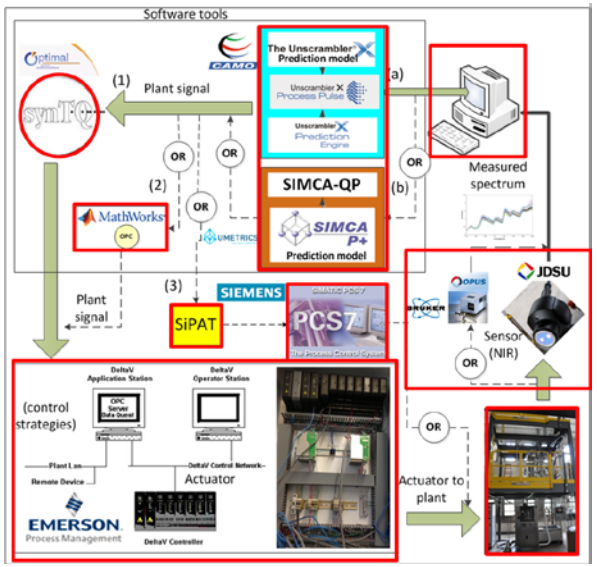
Sensitivity Analysis for a CDC Process

Big Data, Industry 4.0, and Artificial Intelligence

- Utilize advances in machine learning to extract more information from product quality data
  - Explore approaches for explainability and validation of AI based approaches
- Awarded cooperative grant to Rutgers and Purdue Universities on the application of Industry 4.0 to CM
  - Design and implementation of integrated data management and informatics infrastructure for CM
  - Development of process knowledge extraction strategies applied to a CM process for intelligent process monitoring, fault diagnosis, material tracking and real-time risk assessment



Calderon C *et. al.* J. Pharm Sci 2018 (107)



ETT Science and Research Activities: Additive Manufacturing

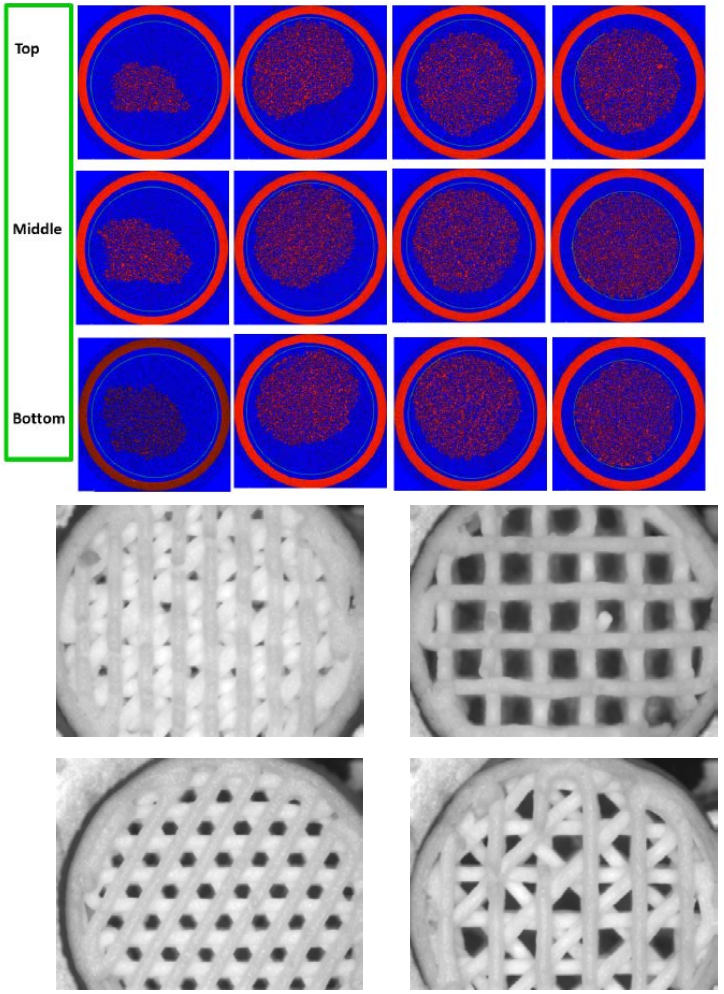
- Platform for precision medicine by delivering the ability to tailor production to different patient populations
  - Opportunities to develop a wider range of doses without extensive alterations of the process, and produce convenience fixed combination dosage forms
- Material selection and controls is a common ETT-Industry discussion area

Extrusion based 3D printer, shared resource (CDER/CBER/CDRH)

2015: FDA approved first 3D printed orodispersible tablet, Spritam® (levetiracetam) for treatment of epilepsy

Evaluation of 3D Printed Tablets

- Developing a risk map for 3D printed tablets using multiple technologies (e.g. inkjet, and extrusion)
  - Screening different types and concentrations of excipients and polymers
  - Powder characteristics, semisolid characteristics; binding mechanisms; control of printing process
- Investigating capability of printing patterns to control product performance

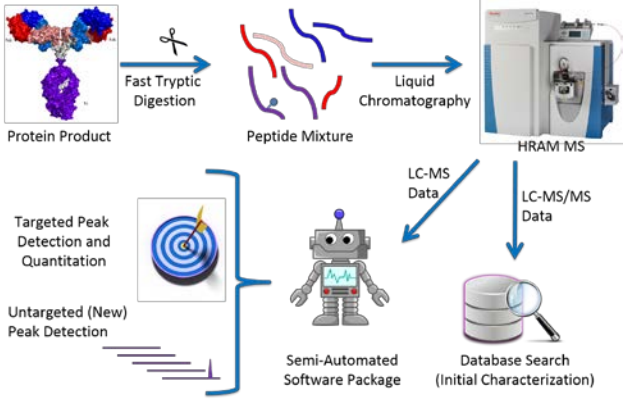


Top: Micro CT scans of 3D printed tablets with different formulations;
Bottom: Printed weaving patterns to control product performance

Multi-Attribute Methods (MAM)

MAM is a peptide mapping based LC-MS approach proposed to replace traditional methods for QC of protein therapeutics

- More detailed information at the molecular level
  - Analysis of site-specific modifications can allow for tighter control
- Can differentiate between species that may overlap using chromatographic approaches
- Tests multiple attributes at once
- New peak detection allows for control of unexpected new modifications
- May lose information at the protein level
- Method development and fit for purpose validation are common ETT-industry discussion areas



Emerging Technology Program: Sustainability

Building sustainability: Next steps

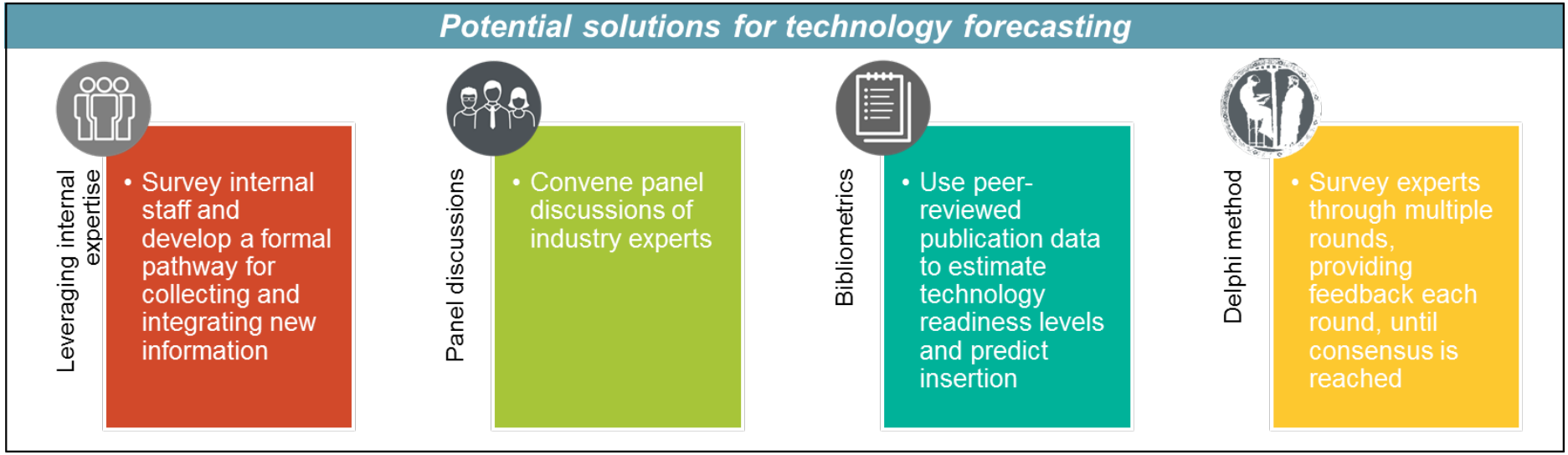
Build a bench of secondary members to accommodate high volume/surge periods.

Strengthen knowledge transfer to spread ETT's technical expertise, institutional knowledge, and cultural values.

Lead international harmonization to align innovative thinking across regulatory agencies worldwide.

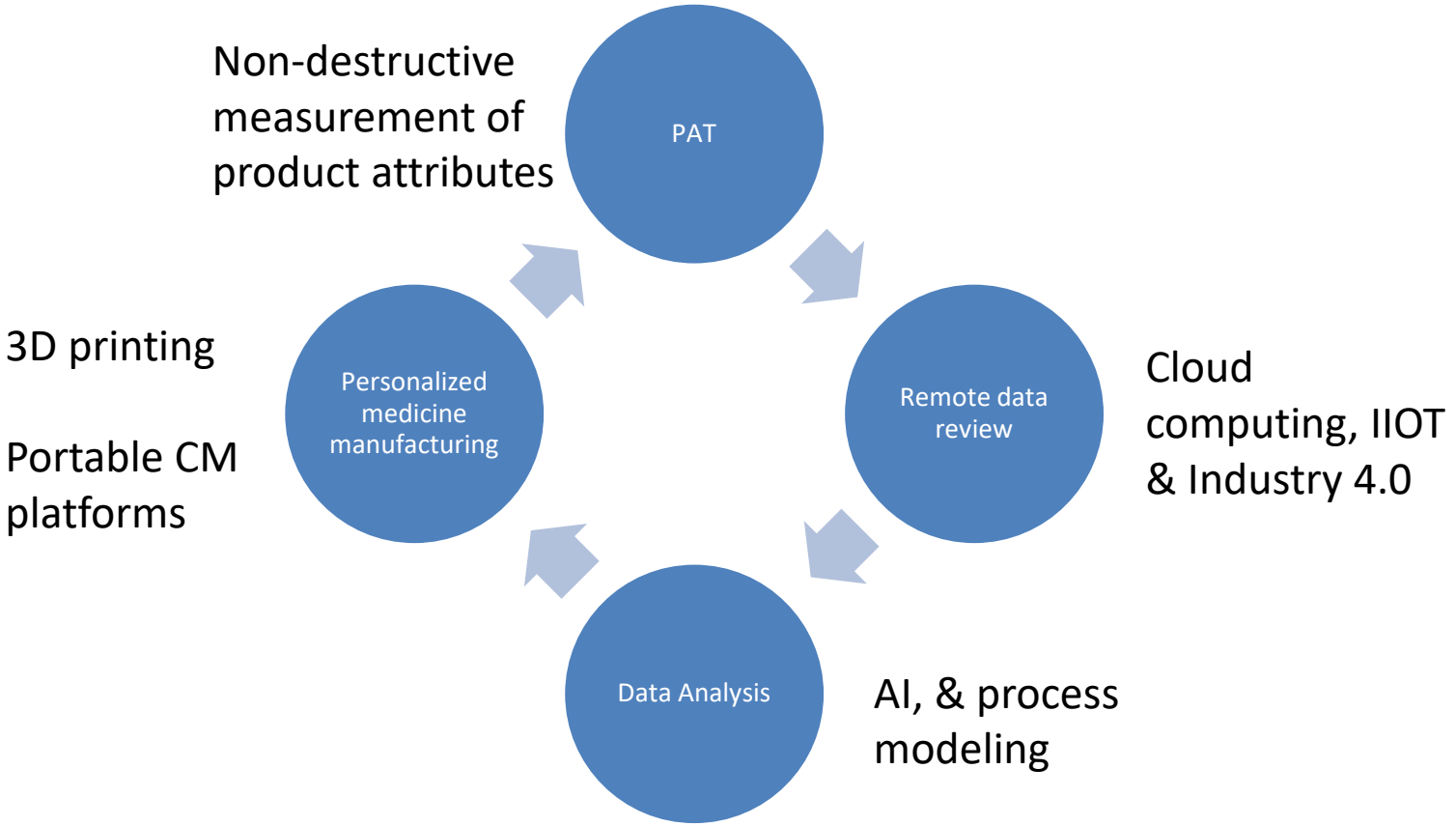
Emerging Technology Program: Continue to Innovate

Working to develop a technology forecast program



ETT leveraging expertise and reach of OPQ's Centers of Excellence (i.e. Manufacturing Science & Innovation and Pharmaceutical Analysis & Characterization) and external relationships to stay abreast of emerging trends in pharmaceutical manufacturing

Journey to the Future of Pharmaceutical Manufacturing?



Multiple emerging technologies can be integrated together to create a new platforms for pharmaceutical manufacturing

Concluding Remarks

- Emerging technologies offer the promise of novel therapies for patients and modernizing pharmaceutical manufacture
- FDA supports the implementation of innovative technologies using a science and risk-based approach
- The OPQ Emerging Technology Program can be utilized for early and effective interactions between FDA and industry in developing emerging manufacturing technologies
- OPQ science and research activities and collaborations are crucial to informing ETT interactions

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