How Process Models can Facilitate Quality Risk Management for Emerging Technologies

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Outline

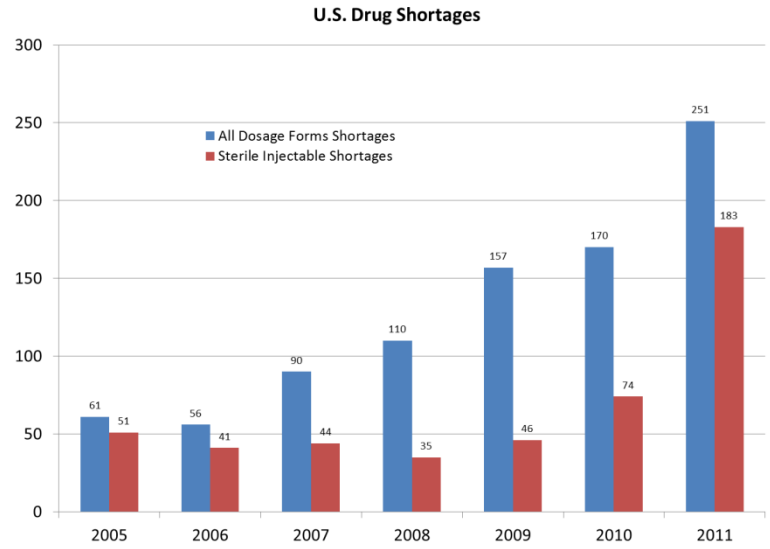
- Initiatives to Support Adoption of Emerging Technologies
  - Emerging Technology Team
  - Regulatory Science Program
- Regulatory Science Initiatives Supporting CM
- Utilization of Models to Support Quality Risk Management
- Direct Compression Case Study
  - Risk Assessment
  - Risk Mitigation
  - Risk Communication
- Concluding Remarks

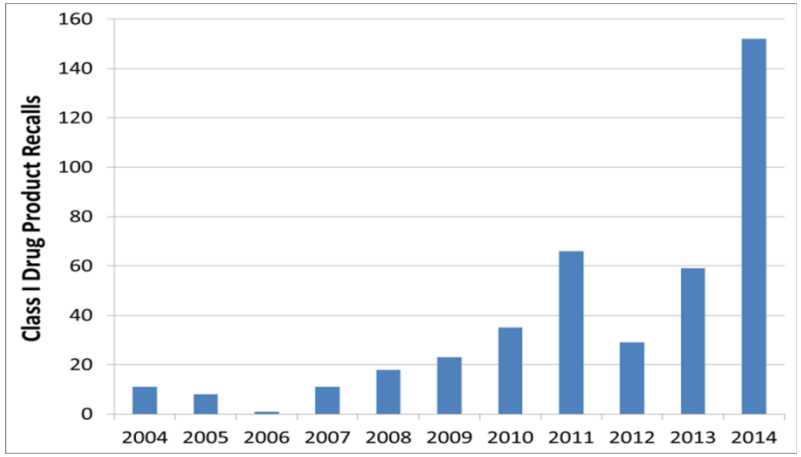
Drivers for Modernizing Pharmaceutical Manufacturing

- Advancing a 21st-Century Vision for Quality

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

- Current Challenges Related to Product Quality





[1]U.S. Food and Drug Administration, "Drug Recalls," [Online]. Available: http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/default.htm

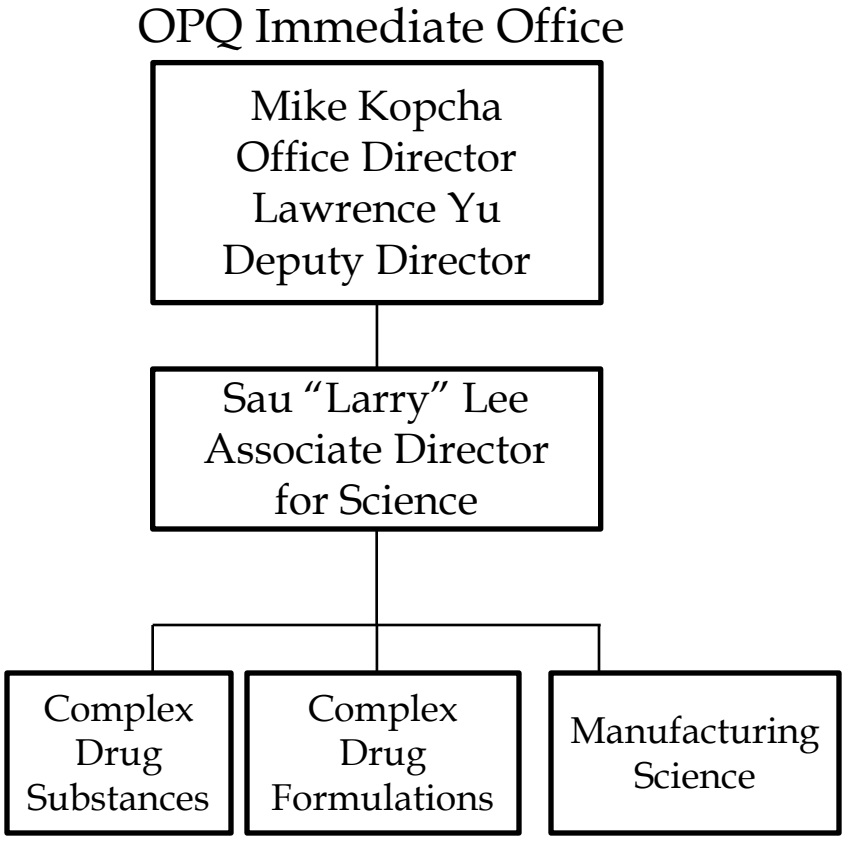
Emerging Technology

- One of OPQ's stated goals is to *Encourage development and adoption of emerging pharmaceutical technology*
- What is an Emerging Technology?
  - Technology that has the potential to modernize the body of knowledge associated with pharmaceutical development to support more robust, predictable, and/or cost-effective processes or novel products and with which the FDA has limited review or inspection experiences, due to its relative novelty
- Examples of Emerging Technology include:
  - Novel methods of manufacturing
    - **Continuous manufacturing of drug substance and drug product**
    - "On-demand" manufacturing of drug products
    - Use of robots in pharmaceutical manufacturing
    - 3-D printed tablets
    - New container and closure system for injectable products

FDA Emerging Technology Team (ETT)

- Vision
  - Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing where the Agency has limited review or inspection experience
- Objectives
  - To serve as a centralized location for external inquiries on novel technologies
  - To provide a forum for firms to engage in early dialog with FDA to support innovation
  - To ensure consistency, continuity and predictability in review and inspection by serving a lead role on the quality assessment team
  - To identify and evaluate roadblocks relating to existing guidance, policy, or practice
  - To help establish review and inspection standards and policy, as needed
  - Contact us: **CDER-ETT@fda.hhs.gov**
- ETT is a small cross functional team with representation from all relevant CDER and ORA review and inspection programs
- Draft Guidance for Industry: Advancement of Emerging Technology Application to Modernize the Pharmaceutical Base, December 2015

OPQ Science and Research Staff (SRS)



- Manufacturing Science Team
  - Manage external research projects (grants and contracts)
  - Develop and implement computational tools to support the risk-based assessment of drug manufacturing processes and quality
  - Interface with quality review teams through the ETT
  - Communication and workshop planning
  - Collaborates and coordinates with OTR & OBP in developing in-house advanced manufacturing lab programs
  - Consults on complex scientific issues with appropriate OPQ office(s)

Regulatory Science Initiatives Supporting CM

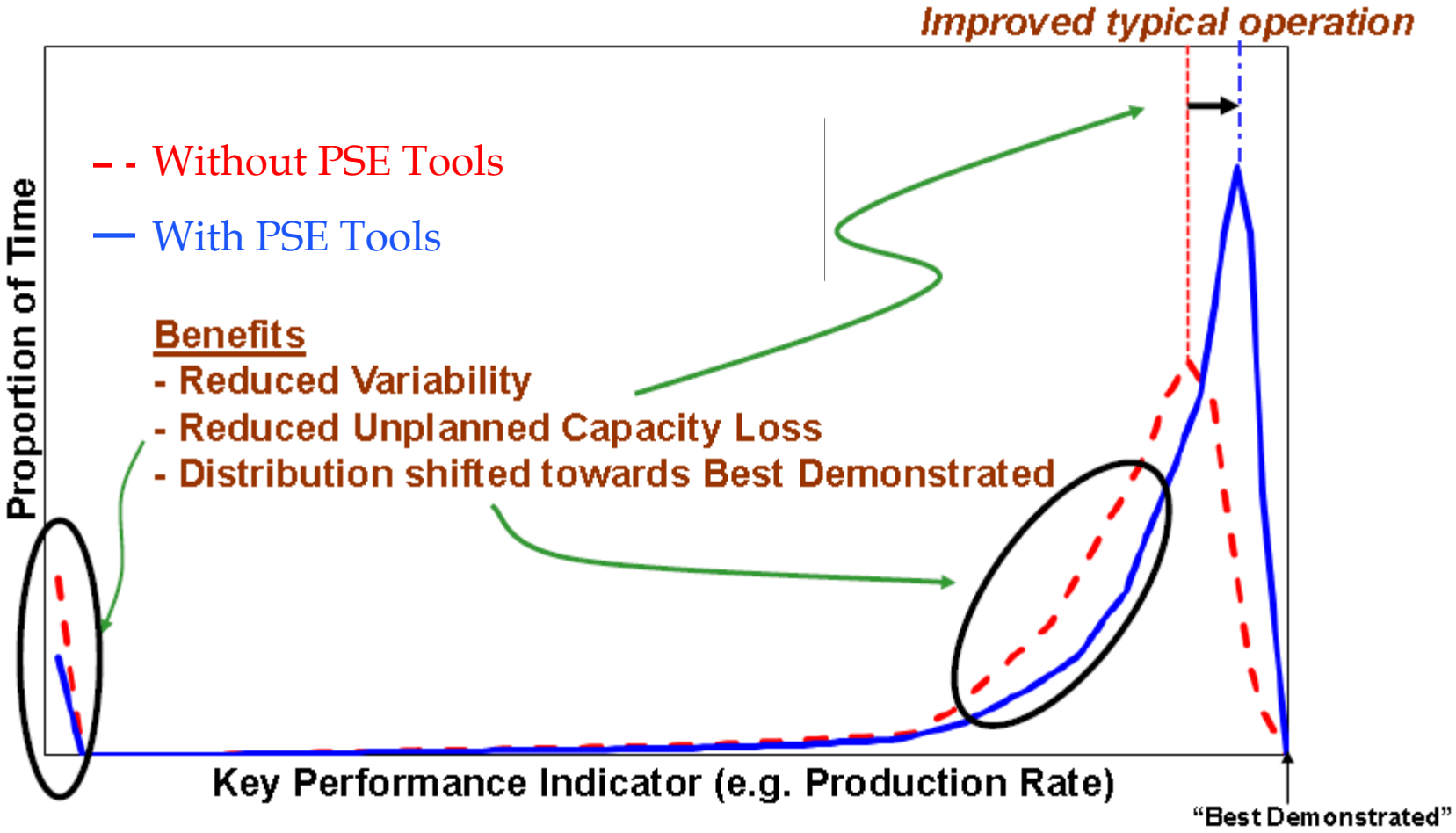
- Enhancing Regulatory Science for the Risk Based Assessment of Emerging Manufacturing Technologies Projects
  1. **Process simulation and modeling tools to facilitate the application of quality risk management**
  2. Investigations into material properties and equipment configurations; linking design space to final product quality
  3. Establishment of knowledge base to assess advanced process control & monitoring approaches (active controls, multivariate statistical process control, etc.)
  4. Concept development for utilizing process and materials data (raw and in-process) that support real-time release testing
- BARDA-FDA Continuous Manufacturing Innovations Initiative
  - Amendment to FDA's Advancing Regulatory Science BAA
- OTR and OBP developing in-house laboratory capability to enhance FDA's knowledge in manufacturing science to support CM implementation

Applications of Process Modeling

- Process models can provide a framework for process design, risk assessment, process control, and optimization
- Process models imbedded in Process Systems Engineering tools can provide benefits throughout the product lifecycle

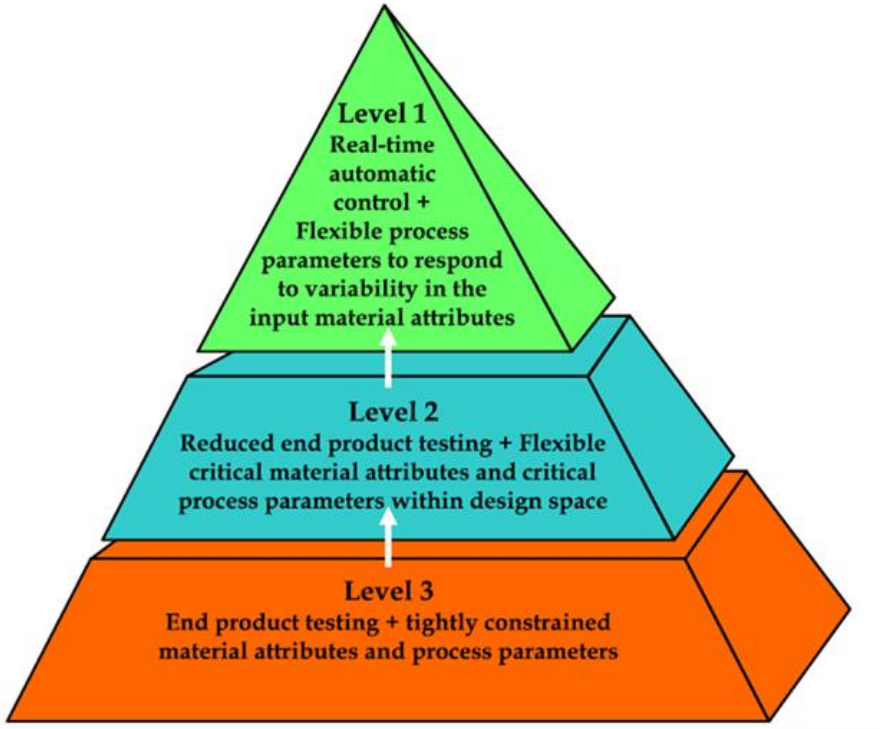
Process Systems Engineering (PSE) Tools	Process Development Objectives
Predictive models	Process Understanding
Flowsheet modeling	Process Integration and Simulation
Feasibility analysis	Operating Space
Steady-state Optimization	Process Design
Dynamic Optimization	Process Efficiency
Sensitivity Analysis	Risk Assessment
Controller Design	Operations Excellence

Why Utilize PSE Tools



Continuous Manufacturing as a Potential Driving Force for PSE Tools

- Inherently data rich processes
- Availability of plant wide information systems
- Advancements in process modeling and simulation



Lee S. *et. al.* J Pharm Innov. **2015** DOI 10.1007/s

Many continuous manufacturing systems promote the adoption of higher level controls, although a hybrid approach combing the different levels of control is viable for some product and process designs

Development of Process Simulation and Modeling Platform

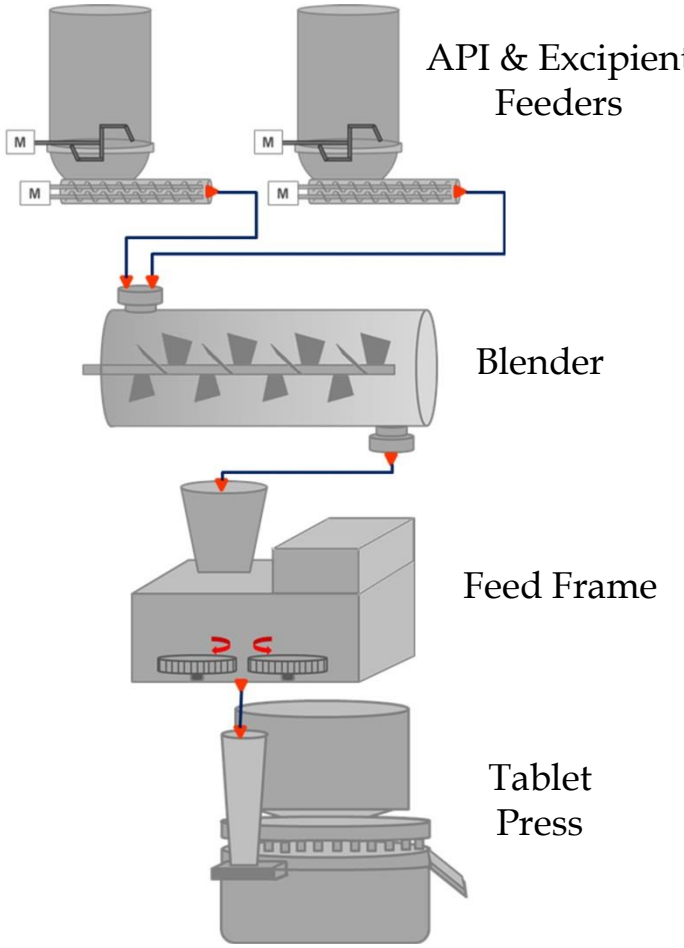
- Utilization of models in a regulatory setting is not new
  - Pharmacokinetics and drug absorption modeling (e.g., GastroPlus simulations)
- However, process modeling of pharmaceutical powder processes is not yet mature and requires further development
  - Advancing the development of unit operation model libraries
  - Integrated process models (i.e. flowsheet models) including process controls
  - Post-processing tools to a facilitate risk assessments
- FDA issued two grants for the development of process simulation and modeling tools for integrated pharmaceutical manufacturing processes
  - Rutgers University
  - University of Massachusetts at Lowell
- Aim of the program is to create a collaborative platform for process simulation
  - Build on process modeling knowledge developed in academia, industry, equipment vendors and regulatory bodies

Process Models as an Emerging Tool to Support Quality Risk Management

- Risk assessment: Models can be utilized to identifying hazards and failure modes
  - Process understanding forms the foundation for effective risk management
- Risk mitigation: Models can be utilized as part of the control and/or used to evaluate the effectiveness of the control strategy
  - Model based control, multivariate monitoring, analysis of large of data sets, and/or Real Time Release Testing (RTRT)
- Risk communication: Process models can be good framework for capturing the related scientific knowledge and communicate residual levels of risk
  - Additional process understanding gained and communicated throughout the lifecycle of the drug product could be utilized as part of continual improvement of the process
- Process models can support the effective implementation of emerging technologies
- Process modeling is one of the approaches to the meet the general expectation of a science and risk-based understanding and control of processes and product quality

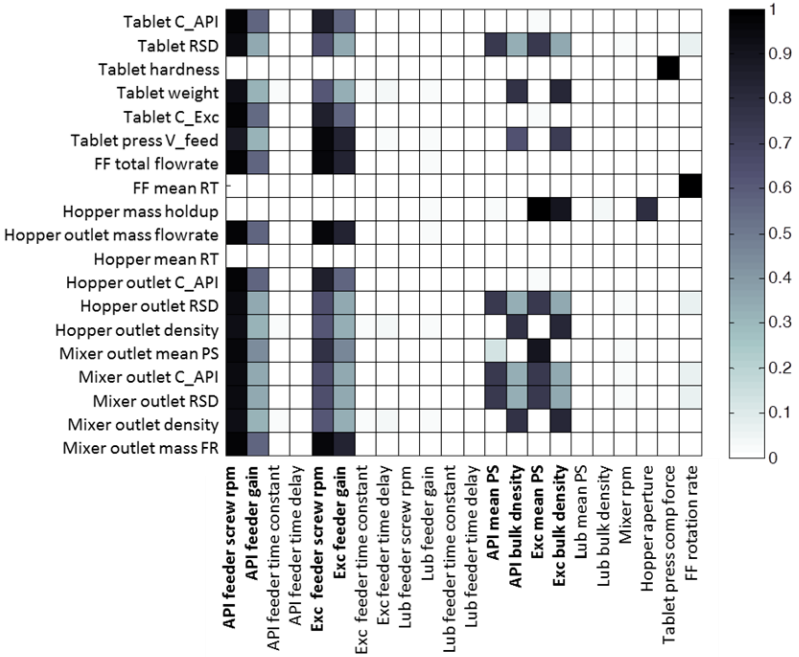
Direct Compression Case Study to Illustrate Research Initiatives

- Many sources of variability in continuous manufacturing process
  - Raw material properties
  - Design parameters
  - Operating conditions
- Applications of sensitivity analysis:
  - Identification of critical process parameters
  - Identification of potential control variables and development of control strategies



Sensitivity Analysis and Risk Assessment

Model Based Risk Assessment for Continuous Process



Current Example of an Initial Risk Assessment Batch Process for IR Solid Oral Drug Product

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	Comment
Physical stability (solid state)	Crystalline (3)	1	4	**12**	BCS class I
Chemical stability	Increasing trend (4)	3	4	**48**	Increasing trend of Related Compound A
Assay	2	3	3	**18**	
Content uniformity	>10% (2)	2	4	**16**	77.8% drug load, wet granulation
Microbial limits	1	3	3	**9**	
Dissolution IR	3	2	2	**12**	

Preliminary screening

- Focus subsequent assessment on most significant parameters
- Feeder parameters - Screw speed; Feed factor

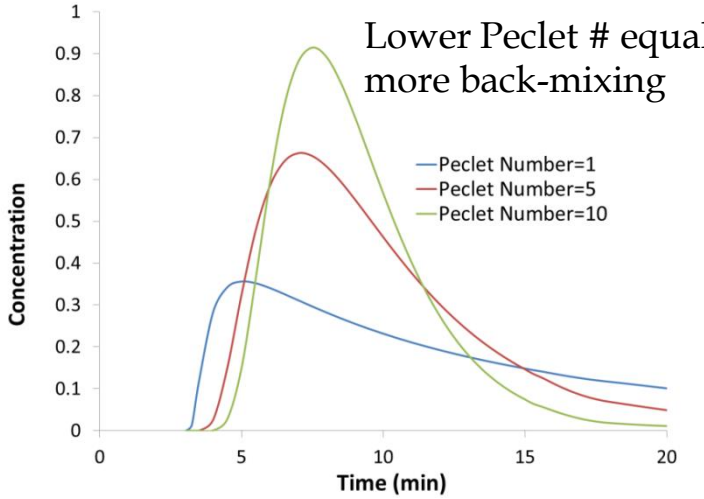
Boukouvala *et. al*. Comput. Chem. Eng. 2012;42;30-47
Lakerveld R *et. al.* AIChE J. 2013;59;3671-3685

Process Understanding: Dynamics

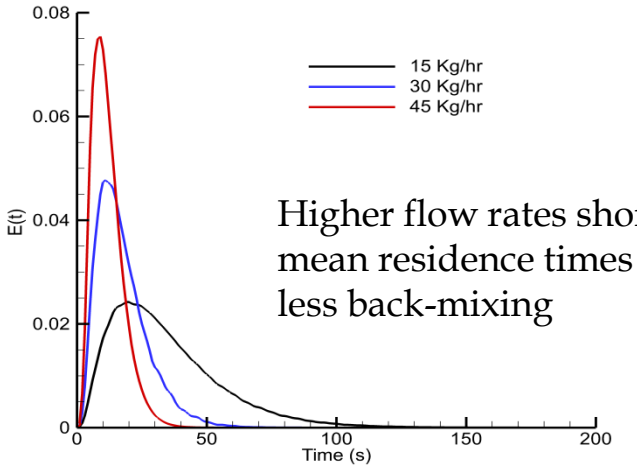
- Understanding the interactions of unit operations in the process train help understand the behavior of the entire system (over time)
- Residence Time Distribution (RTD) depends material properties, process parameters, & equipment configuration

Line rate is a important variable to be considered

RTD as a function of back-mixing



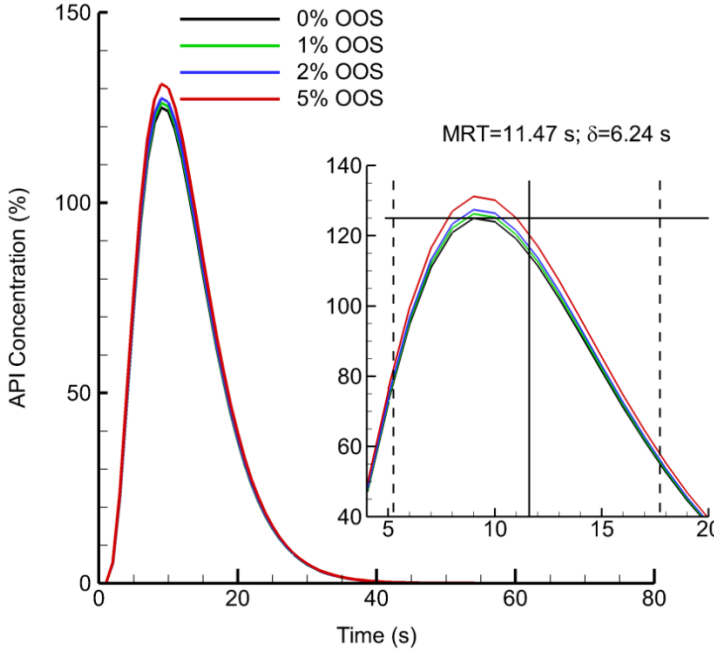
RTD as a function of line rate



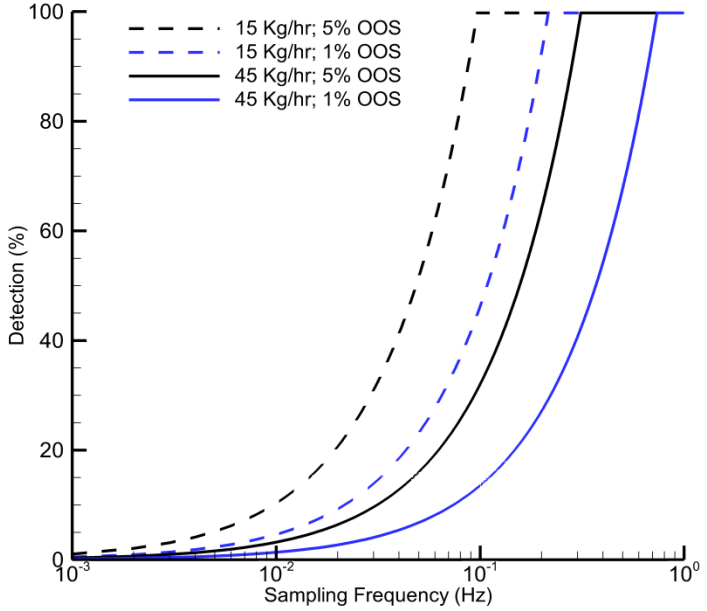
Process Dynamics – Detecting Disturbances

- Detectability of transient disturbances impacted by relationship between process dynamics and sampling frequency

API concentration pulses resulting in OOS material



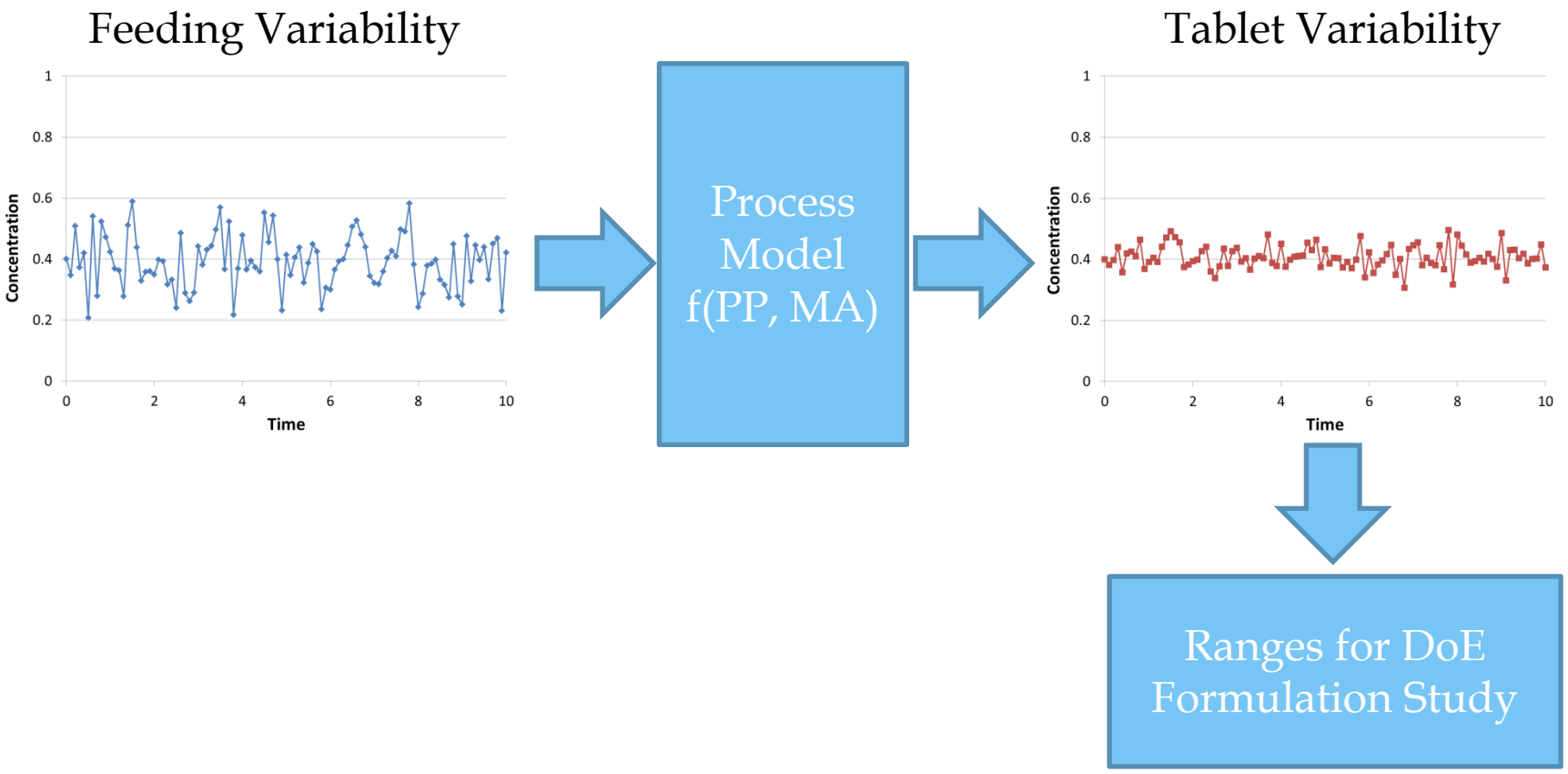
Impact of RTD on Detectability



Engisch W. and Muzzio F.. J Pharm Innov. 2015; DOI 10.1007/s12247-015-9238-1

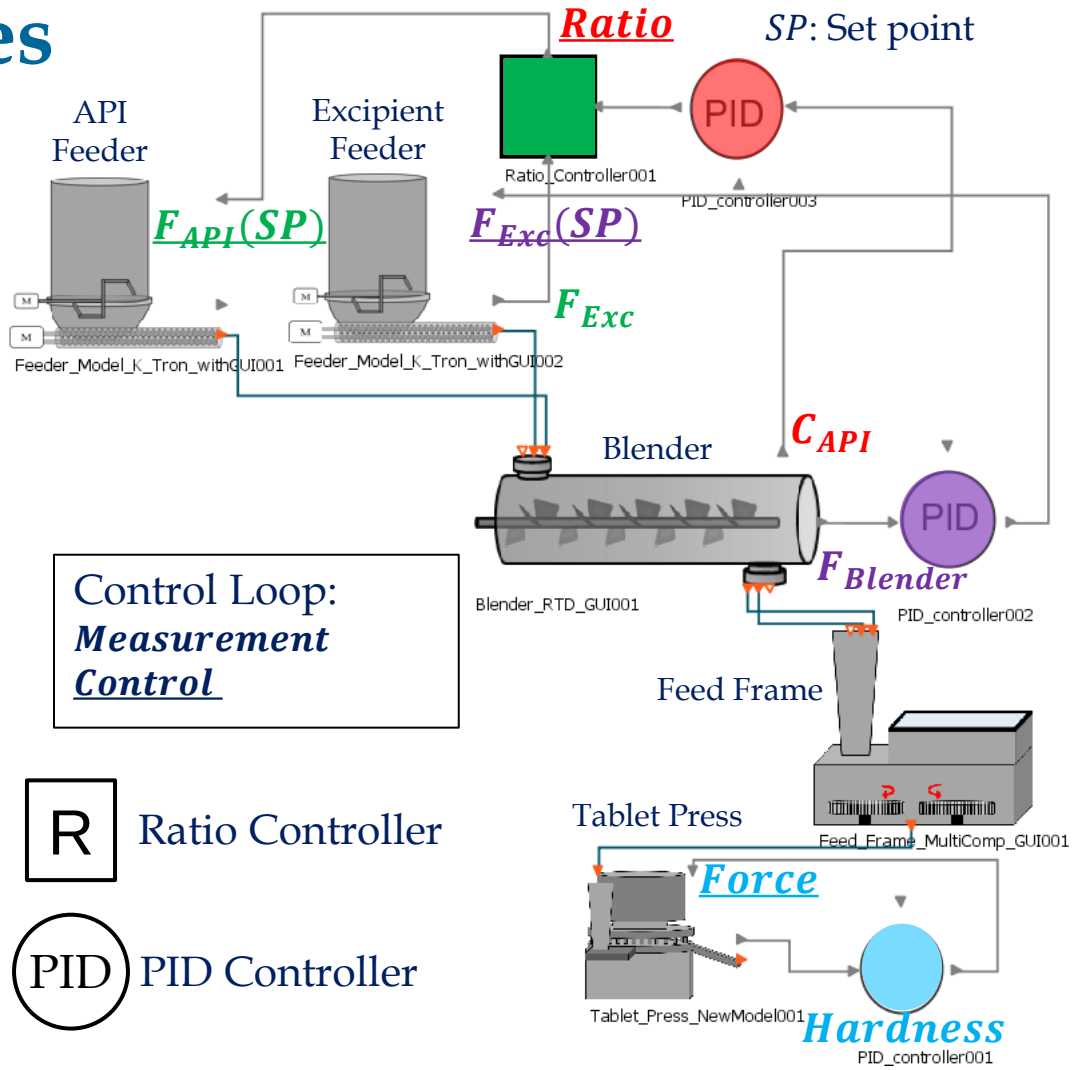
Process Dynamics – Formulation Variability

- Feeding variations of excipients may impact product performance (e.g. dissolution)



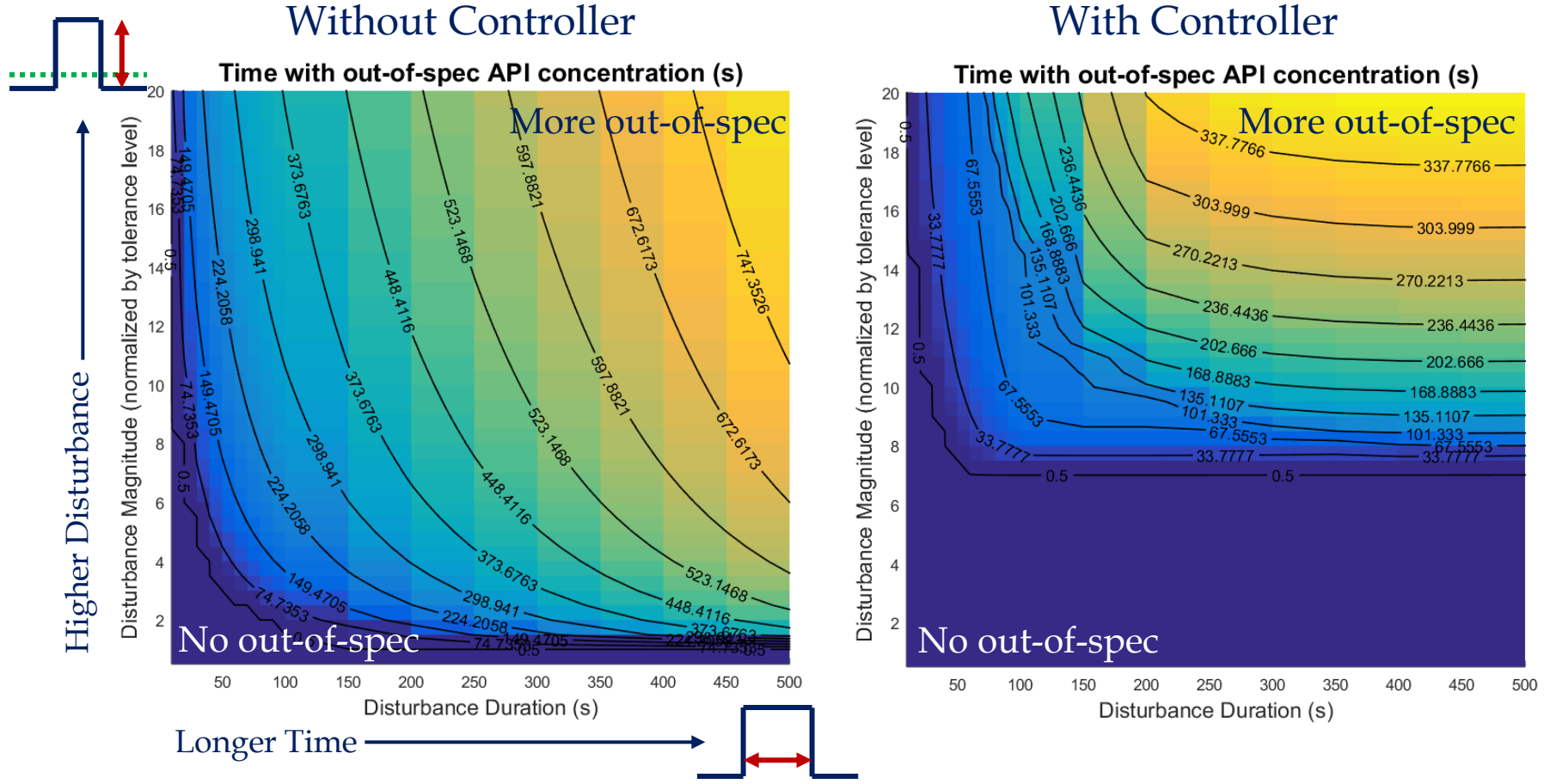
Risk Mitigation - Advanced Control Approaches

- Control Strategy approaches can be incorporated into the flowsheet model
- Ratio Control: used to maintain the flow rate of one stream at a specified proportion relative to another flow rate
- Feedback: output information (controlled variable) is used to automatically trigger upstream action (manipulated variable)
  - Typically incorporated into the control of individual unit operation (e.g. loss-in-weight feed rate control, compression force control)



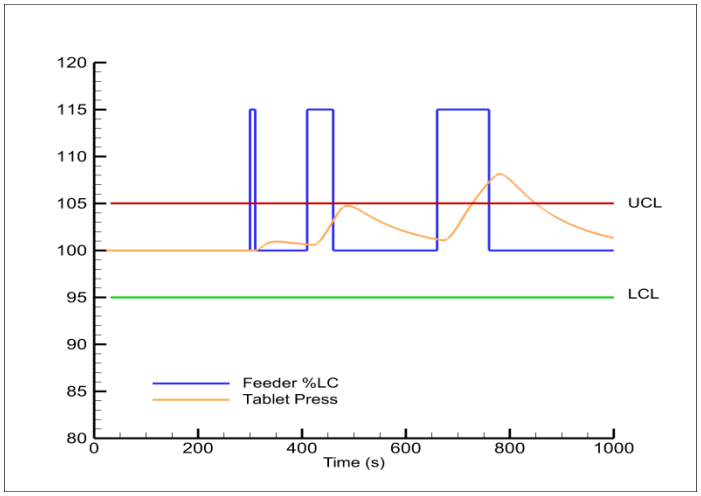
Case Study Evaluating Control Strategy

- Time with out-of-spec API concentration: API feeder disturbance



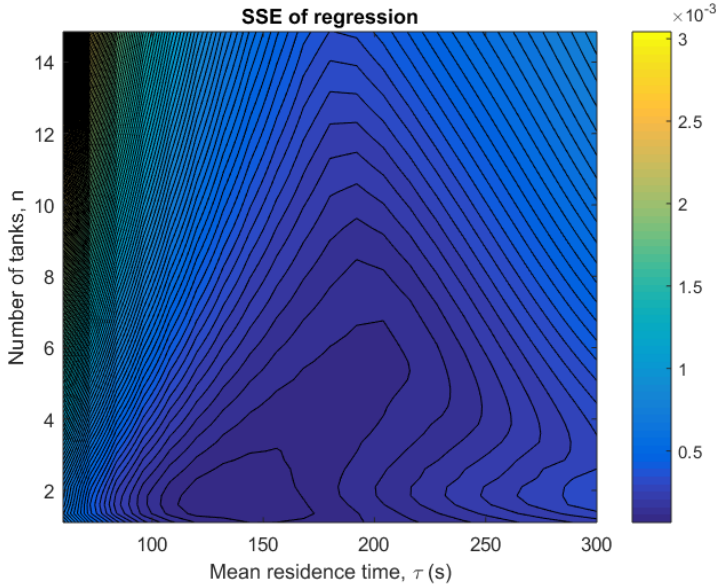
Risk Mitigation – Utilizing Models to Divert of Nonconforming Material

- The evaluation of overall residence time distribution and the understanding of propagation of a disturbance between extraction points in the system are important to justify the amount of material at risk due to an unexpected even or disturbance
  - Analysis should account for uncertainty in the measured/predicted RTD



Tank in Series Model for RTD

$$E(t) = \frac{t^{n-1}}{(n-1)!\left(\frac{\tau}{n}\right)^n} e^{\left(\frac{-nt}{\tau}\right)}$$



2-D contour of minimized SSE for RTD model

Scientific and Risk-Based Considerations for Model Based Material Diversion

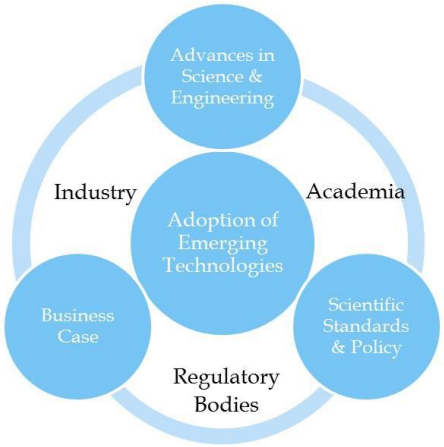
- Develop the model utilizing scientifically sound principles and conditions that directly reflect routine commercial production
- Verify performance for high-impact models
  - E.g. Capability of the model to trace the identified OOS product segment through the system to the rejection point
- Understand risks to validity of model predictions
  - Model parameter uncertainty
  - Expected variation in process parameters and material attributes *including line rate*
  - Assessment of product quality risks resulting from potential transient disturbances and/or process failure modes that may not be identified by or included in the model
- Include model maintenance approaches within the quality system as part of a lifecycle approach
  - Routine monitoring to verify performance

Risk Communication: Process Models

- Quality risk management requires product and process knowledge to identify, analyze, evaluate, control, and communicate the risks
- Process models can be good framework for capturing the related scientific knowledge
  - Formally stating assumptions and reasonable sources of uncertainty enhances confidence in this output and/or helps identify its limitations
  - Utilization of process models in risk-based quality management can become one source of common risk assessment approaches, and can be used to facilitate the communication of risk and risk mitigation approaches between industry and regulatory bodies

Concluding Thoughts

- OPQ supports the modernization of manufacturing in part through the ETT and the advancement of regulatory science
- Continuous manufacturing is a potential driving force for utilization of process model throughout a product lifecycle
- FDA has several ongoing research initiatives on advancing process modeling related to CM
- Process models are an emerging tool to support systematic risk management for pharmaceutical processes
- Interested in developing collaborations to address barriers



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OPQ Science and Research Staff

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Emerging Technology Team

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- Members: Thomas O'Connor(OPQ/IO-SRS), Celia Cruz (OPQ/OTR), Mohan Sapru & Ray Frankewich (OPQ/ONDP), Geoffrey Wu (OPQ/OLDP), Kurt Brorson (OPQ/OBP), Grace McNally, Sharmista Chatterjee & Bryan Riley (OPQ/OPF), Rebeca Rodriguez & Susanne Richardson (ORA)

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