Opportunities and Challenges for the Application of Process Modeling and Simulation for Product Quality Risk Management

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US FDA Center for Drug Evaluation and Research

Pharmaceutical Process Analytics Roundtable (PPAR)
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Disclaimer

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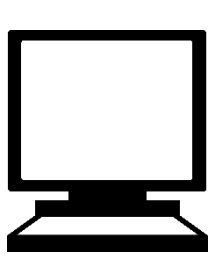
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

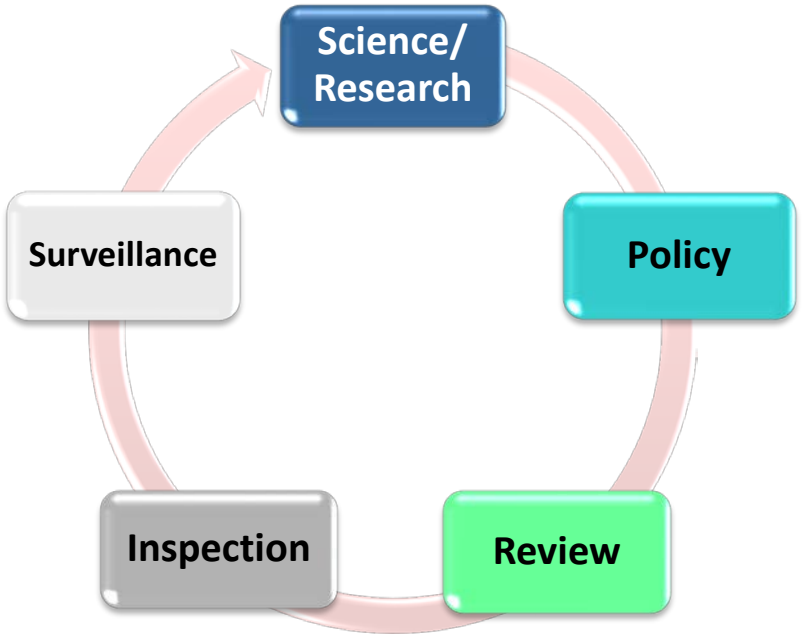

It is what gives patients confidence
in their *next* dose of medicine.

Why is research needed for CDER in Pharmaceutical Quality?

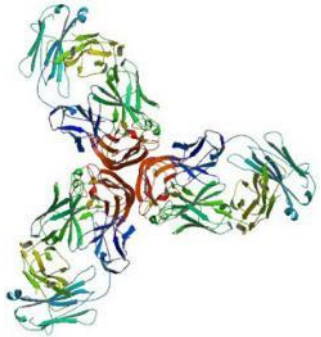
There is increased public awareness of importance for pharmaceutical quality.

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**.



Office of Testing and Research Key Research Areas



1. Manufacturing Science and Innovation
2. Drug Quality Standards and Linkage to Clinical Performance
3. Advanced Characterization of Complex Molecules
4. Physicochemical Characterization of Complex Formulations and Dosage Forms
5. Post-Market Product Quality and Public Health Issues

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.

Mission

Emerging Technology Program

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

ETP Website

Program 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

To engage international regulatory agencies to share learnings and approaches

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

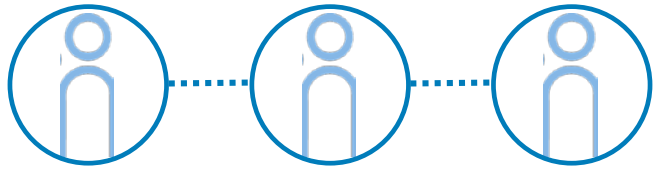
To facilitate knowledge transfer to relevant CDER and ORA review and inspection programs

To help establish scientific standards and policy, as needed

Contact us: CDER-ETT@fda.hhs.gov

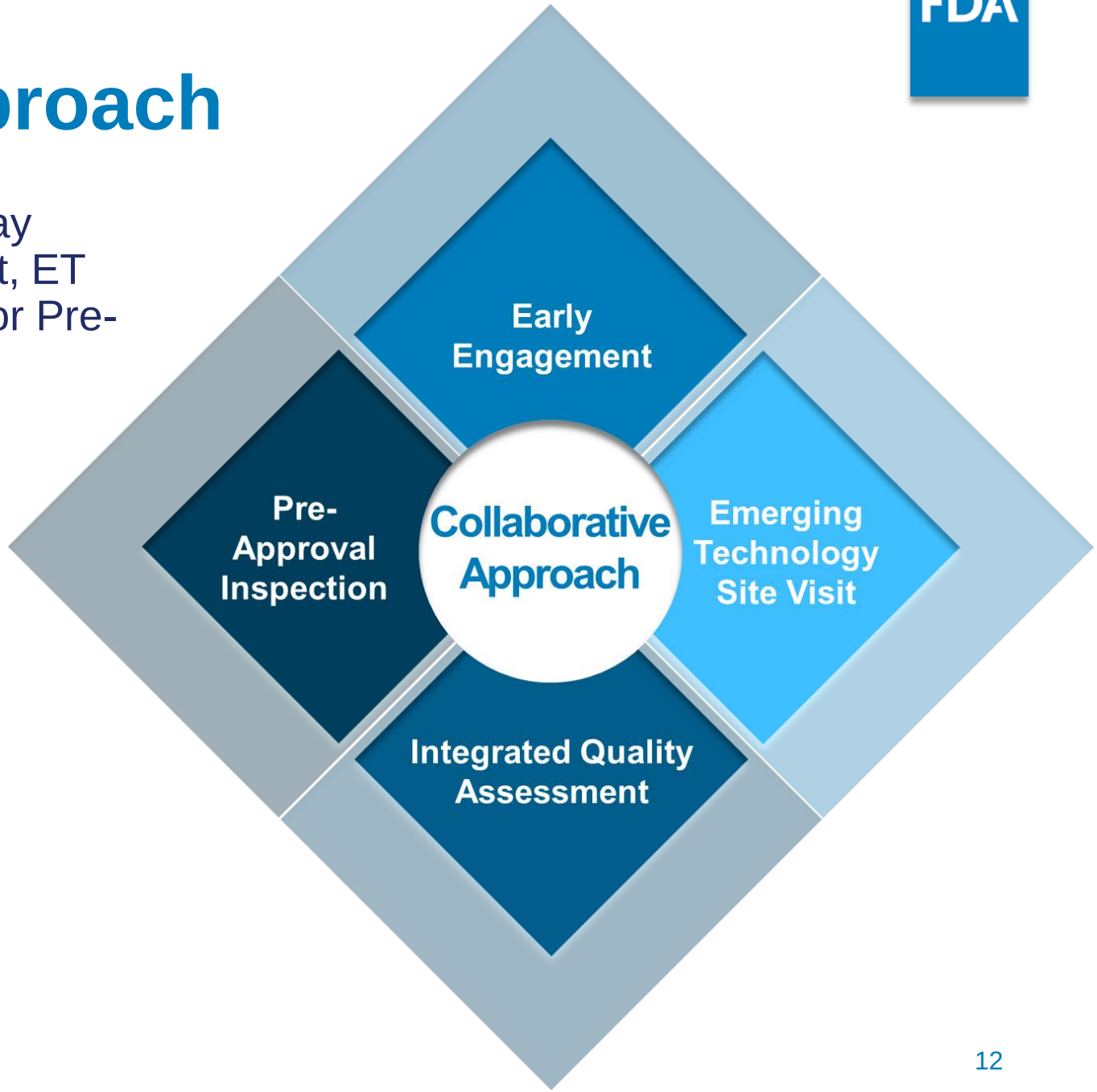
ETT Collaborative Approach

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



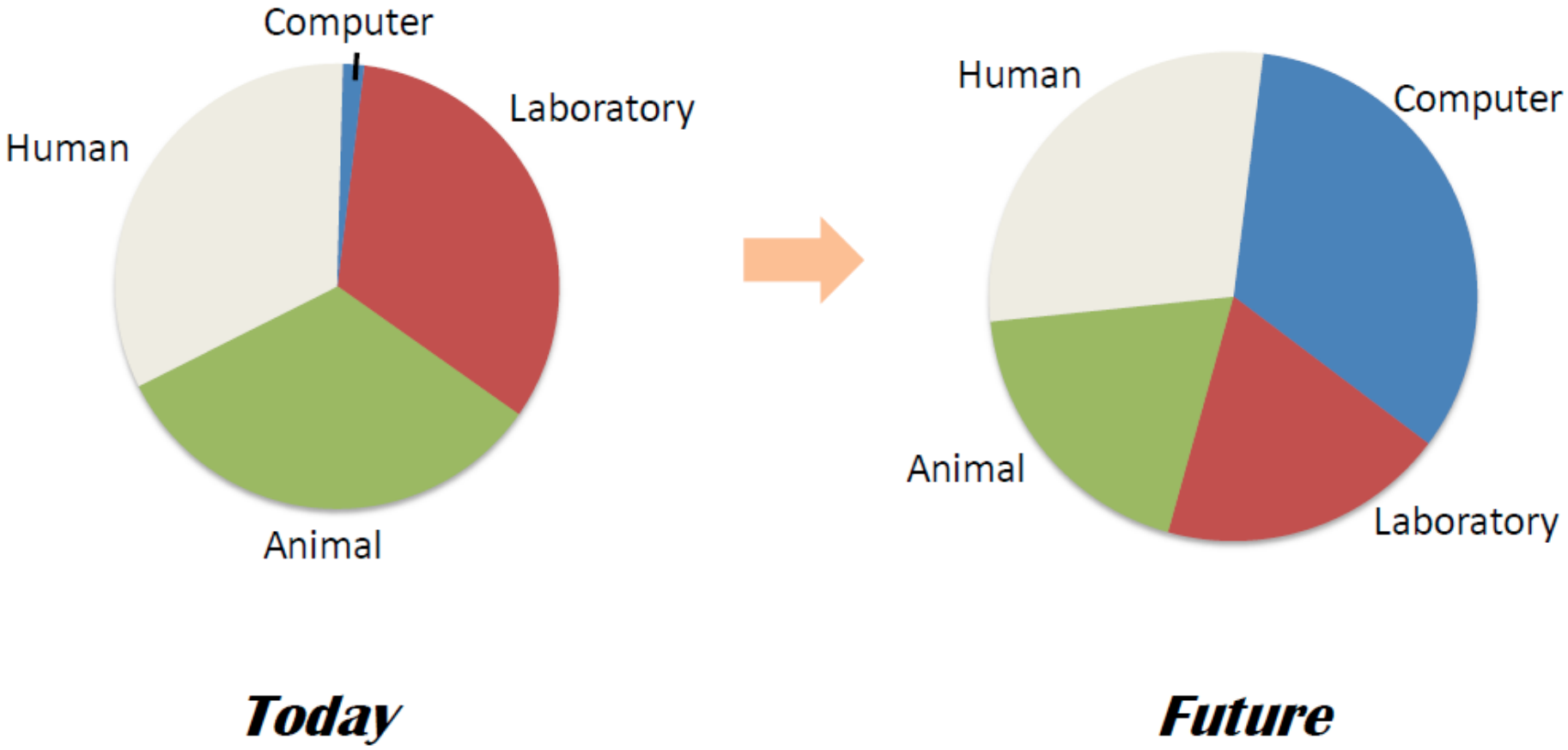
The same ETT representative(s) will be involved in the entire process

The composition of a review team will likely remain the same throughout the entire process



Product Quality Modeling

Sources of Scientific Evidence



FDA Document: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

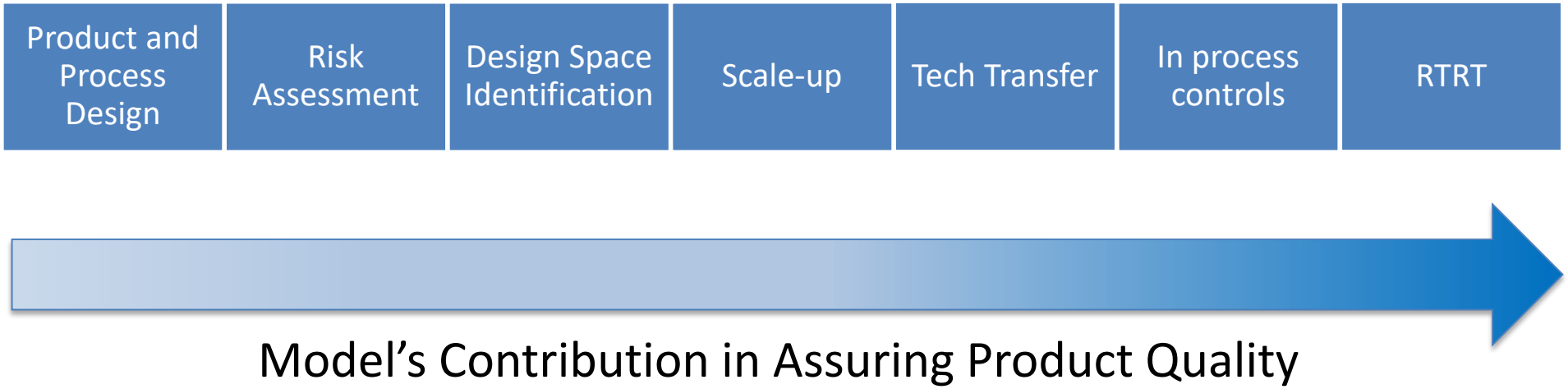
FDA Modeling and Simulation (M&S) Working Group

- Numerous modeling and simulation approaches at the FDA to support decision making
- Working group objectives
  - Raise awareness about M&S to advance regulatory science for public health
  - Foster enhanced communication about M&S efforts among stakeholders
- Working group has over 200 members across all Centers

Chemical	Mechanistic	Statistical	Physics	Big Data	Risk Assessment
• QSAR • Chemometrics • Quality by Design • Molecular docking	• PK/ADME • PK/PD • Lumped parameter • Systems modeling	• Stochastic • Bayesian & adaptive • Monte Carlo • Population modeling • Social network analysis	• Acoustics • Electromagnetics • Fluid dynamics • Heat Transfer • Optics • Solid mechanics	• Next gen sequencing • Ontological modeling • Natural language processing • Machine learning	• Probabilistic risk estimation • Agent based • Quantitative benefit-risk modeling

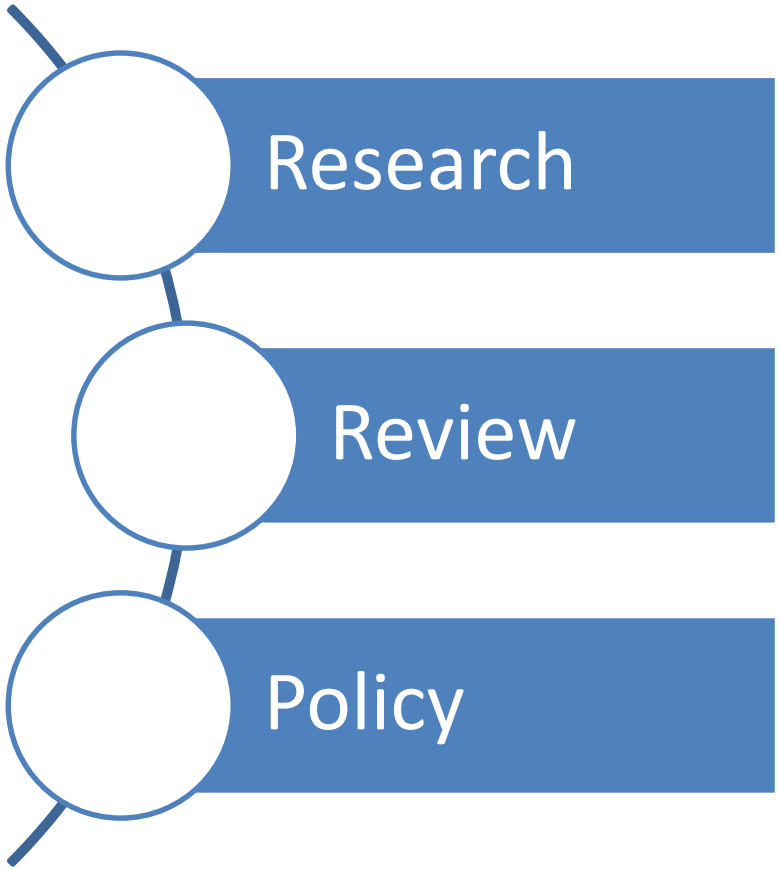
What about the Role of Model for Pharmaceutical Quality?

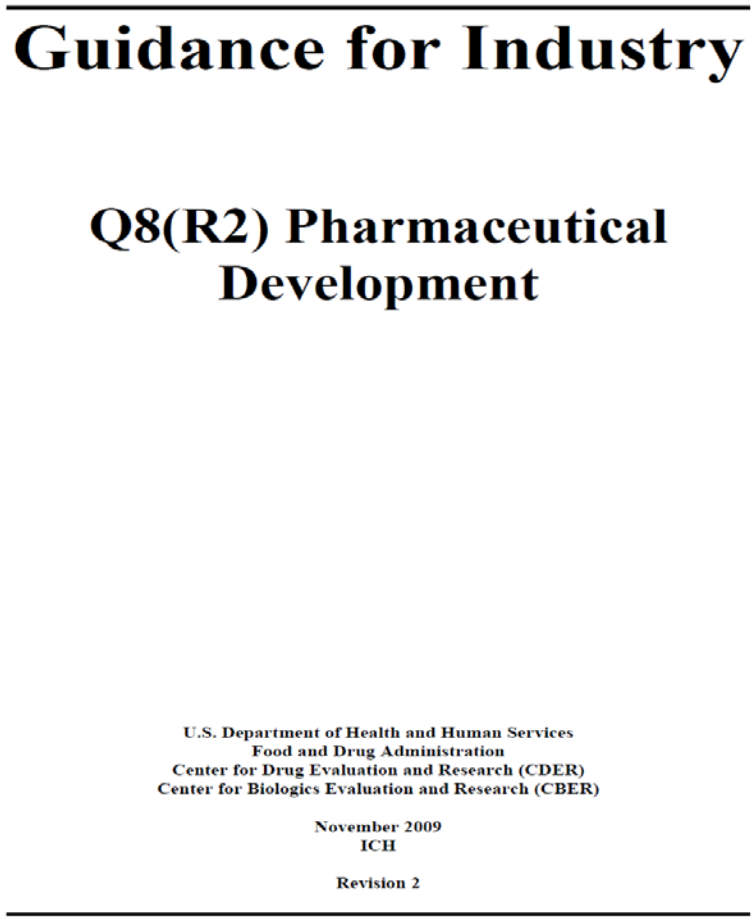
- In Quality by Design framework, mathematical models can be utilized at every stage of product development and manufacturing
- Predictive models have been implemented for developing and controlling processes and have appeared in regulatory submissions
  - Dissolution models for release
  - Multivariate statistical model for residual solvent monitoring
  - Chemometric models for PAT and product release



Response Surface Modeling Experience

Extensive industry and FDA experience with response surface models including research, review, and policy





Guidance for Industry

Q8(R2) Pharmaceutical Development

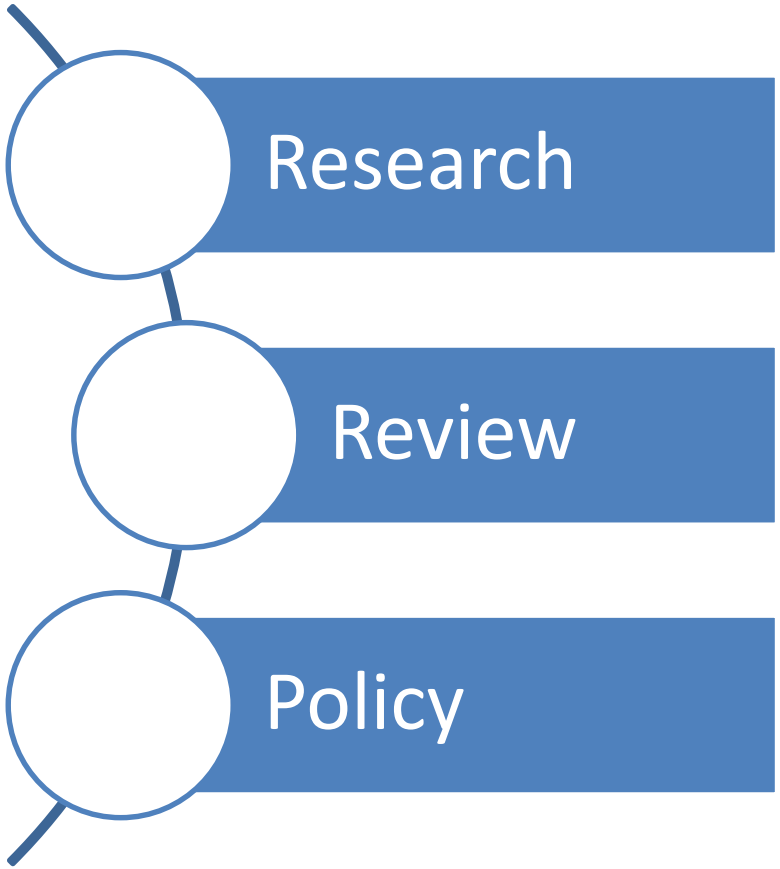
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

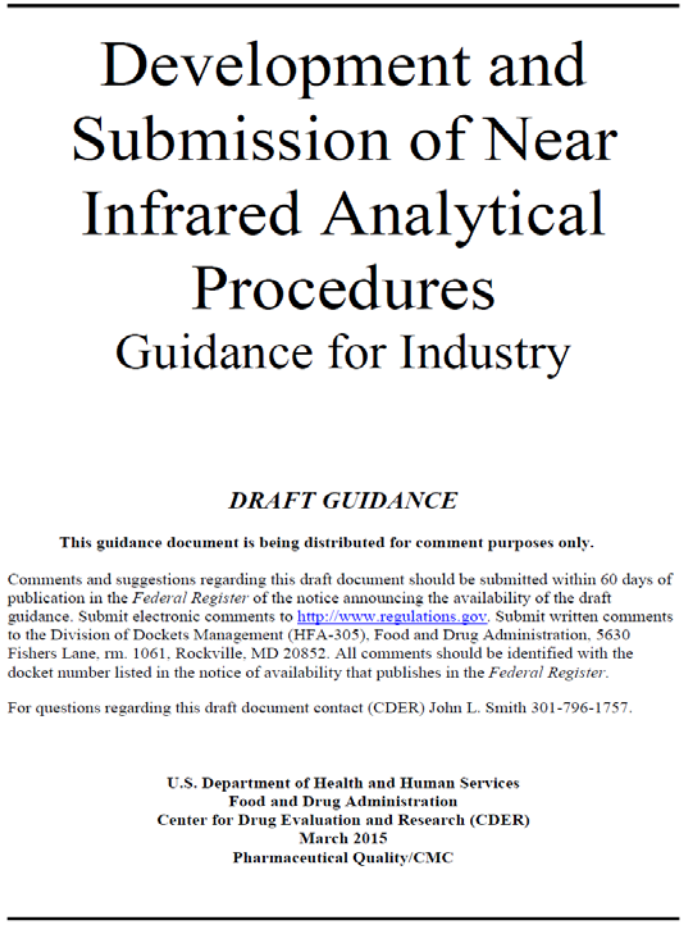
November 2009
ICH

Revision 2

Chemometric Model Experience

Extensive industry and FDA experience with chemometric models for spectroscopy including research, review, and policy





Development and Submission of Near Infrared Analytical Procedures

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) John L. Smith 301-796-1757.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2015
Pharmaceutical Quality/CMC

Modeling Benefits and Challenges

Models provide major benefits to process evaluation and quality assessment, but sometimes challenges may hinder their application

Advantages

1. Establish input and output relationships (CPPs to CQAs)
2. Extract information from large data sets
3. Accelerate development
4. Improve process design and performance
5. Risk assessment of changes prior to implementation
6. Facilitate implementation of process control and optimization

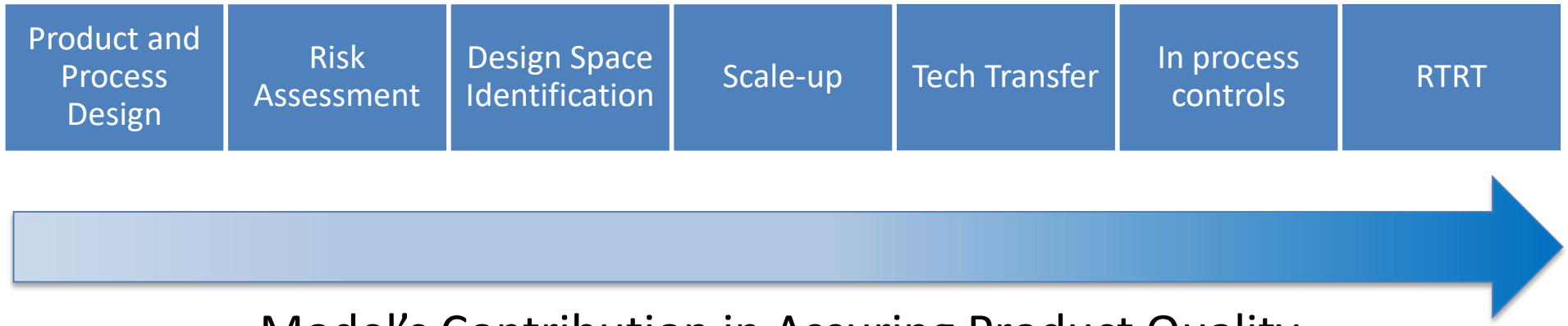
Challenges

1. Data
2. Incomplete mechanistic knowledge
3. *Model verification and validation*
4. *Lifecycle maintenance*
5. Skills and resources for developing models

Evolution of Process Modeling: Regulatory Perspective

- Development and assessment of process models by OPQ is not unprecedented but the frequency, types of models, and applications are evolving

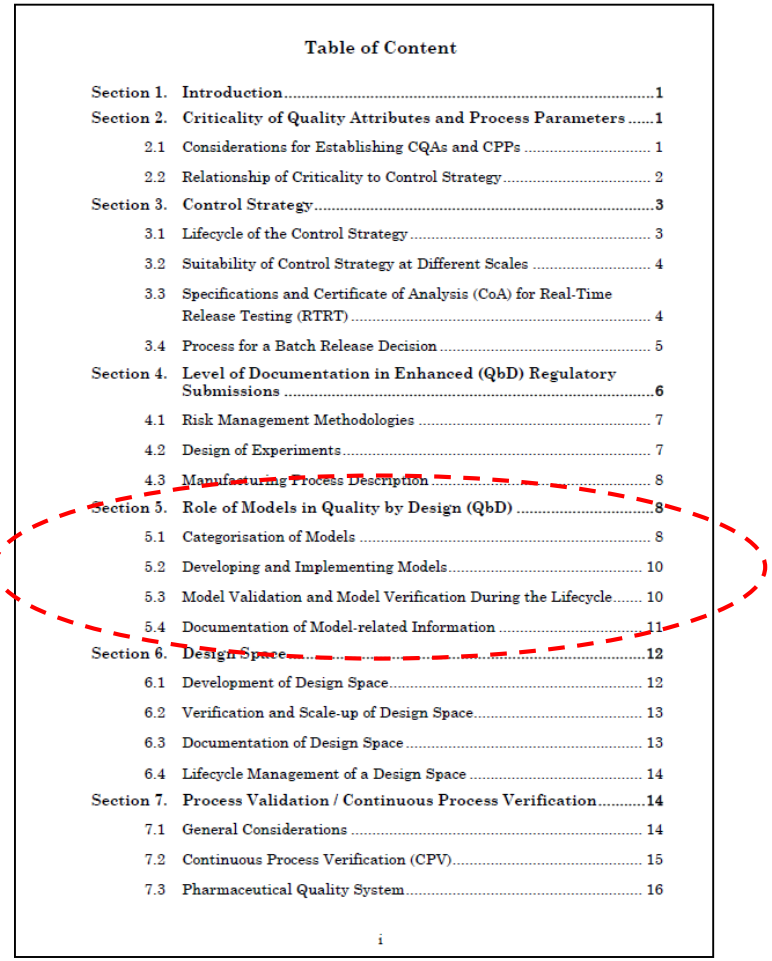
- Advanced manufacturing a potential driving force for utilization of process modeling
  - Inherently data rich processes
  - Availability of plant wide information systems
  - Implementation of advanced control strategy approaches (MPC, RtR, etc.)



Model Guidance

Current Regulatory Framework

ICH Points to Consider Document



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Categorization of Models

High Impact Models
Prediction from the model is the sole indicator of quality of the product, e.g. chemometric model for assay

Medium Impact Models
Important for assuring quality of the product but are not the sole indicators of quality, e.g. model to define a design space

Low Impact Models
Typically used to support process development efforts, e.g. formulation optimization model

- Provides recommendation on documentation based on impact.
- Provides high level guidance on model validation but does not differentiate based on model impact

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf

Draft NIR Guidance

- Recommendations for validation of NIR analytical procedures:
  - Information on the external validation set:
    - Information about the respective batches, including batch number, batch size, and number of samples from each batch used to create the external validation set.
    - For quantitative procedures, distribution of the reference values in the external validation set
  - Validation of a quantitative procedure, including specificity, linearity, accuracy, precision, and robustness, as appropriate
  - Validation of a qualitative method, including specificity
  - Information on the reference analytical procedure and its standard error.
  - Data to demonstrate that the model is valid at commercial scale (e.g., use of commercial scale data during procedure development)
  - High level summary of how the procedure will be maintained over the product's life cycle
- While this guidance is written specifically for NIR, the fundamental concepts of validation can be applied to other PAT technologies

Ten “Not so Simple” Rules for Credible Practice of M&S in Healthcare

- Rules developed by a multidisciplinary committee facilitated by the Interagency Modeling and Analysis Group[1]
  1. Define context clearly
  2. Use appropriate data
  3. Evaluate within context
  4. List limitations explicitly
  5. Use version control
  6. Document adequately
  7. Disseminate broadly
  8. Get independent reviews
  9. Test completing implementations
  10. Conform to standards

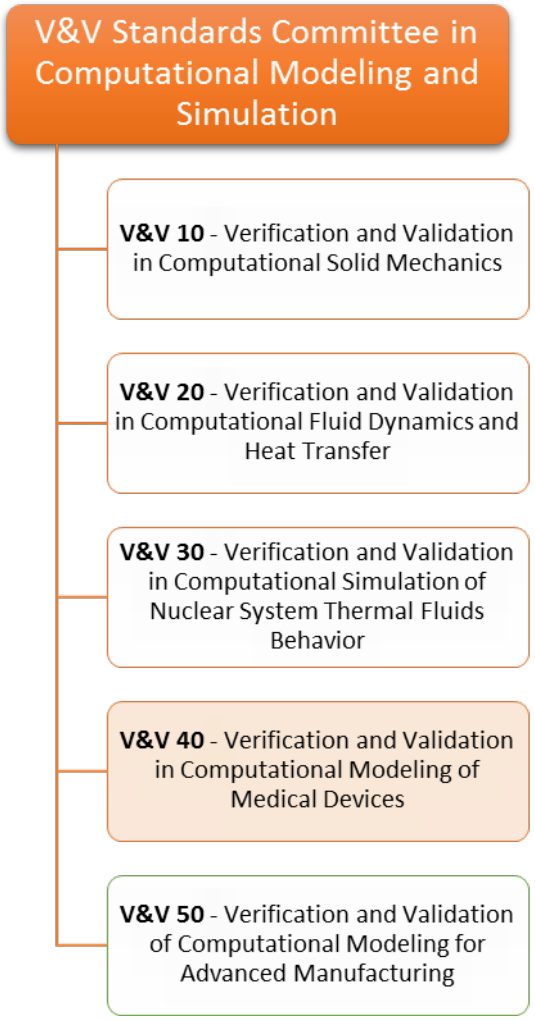
These rules are considered ***"not so simple"*** as their implied meanings may vary, indicating the need for clear and detailed descriptions during their application.

[1]Erdemir, A. *et. al.* 2015 BMES/FDA Frontiers in Medical Device Conference

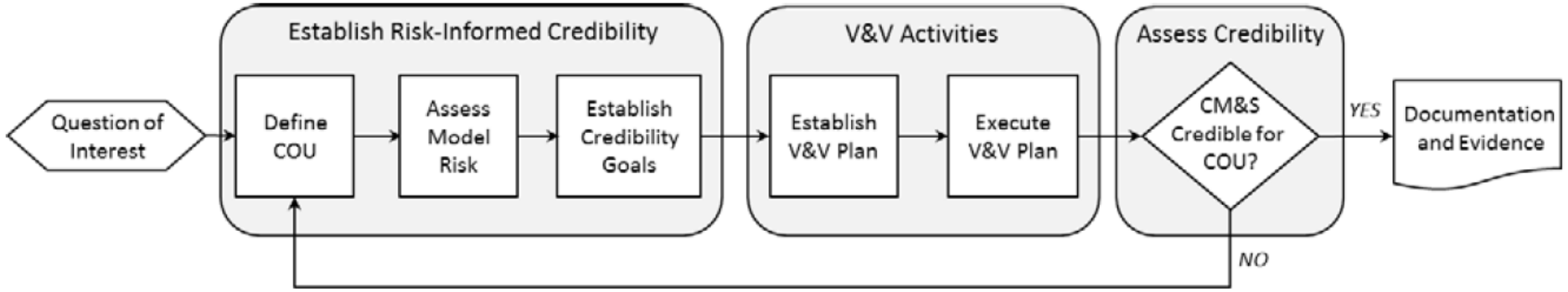
ASME Verification and Validation (V&V) 40

- ASME V&V 40 Charter
  - Provide procedures to standardize verification and validation for computational modeling of medical devices
  - Charter approved in January 2011
  - Standard published January 2019
- Motivating factors
  - Regulated industry with limited ability to validate clinically
  - Increased emphasis on modeling to support device safety and/or efficacy
  - Use of modeling hindered by lack of V&V guidance and expectations within medical device community

Standard applicable to all types of mechanistic models.



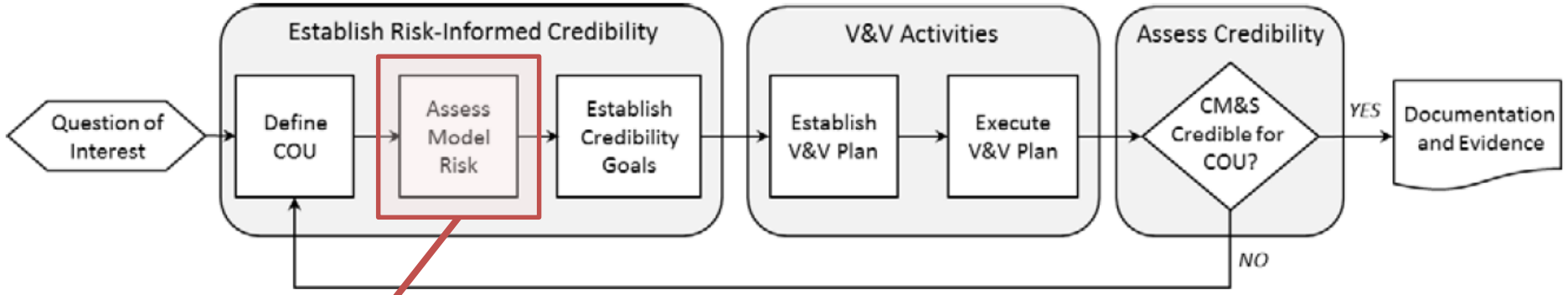
Risk-Informed Credibility Assessment Framework

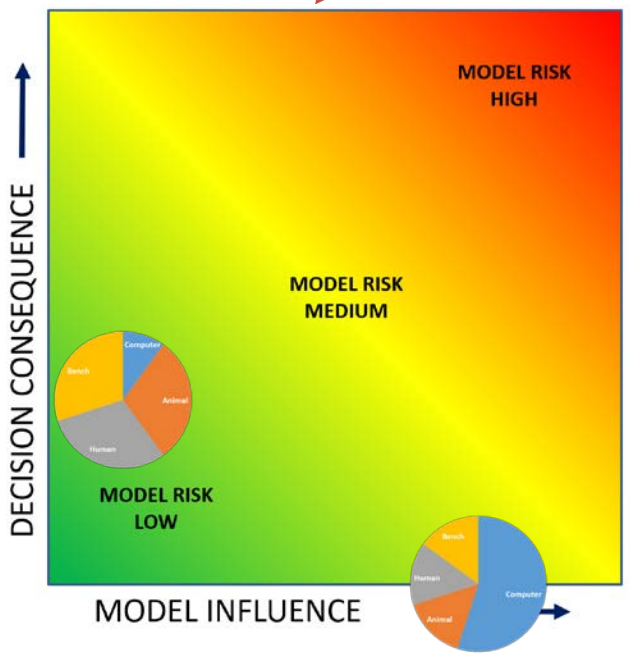


The V&V40 guide outlines a process for making risk-informed determinations as to whether M&S is credible for decision-making for a specified context of use.

- The **question of interest** describes the specific question, decision or concern that is being addressed
- **Context of use** defines the specific role and scope of the computational model used to inform that decision

Modeling Risk Assessment



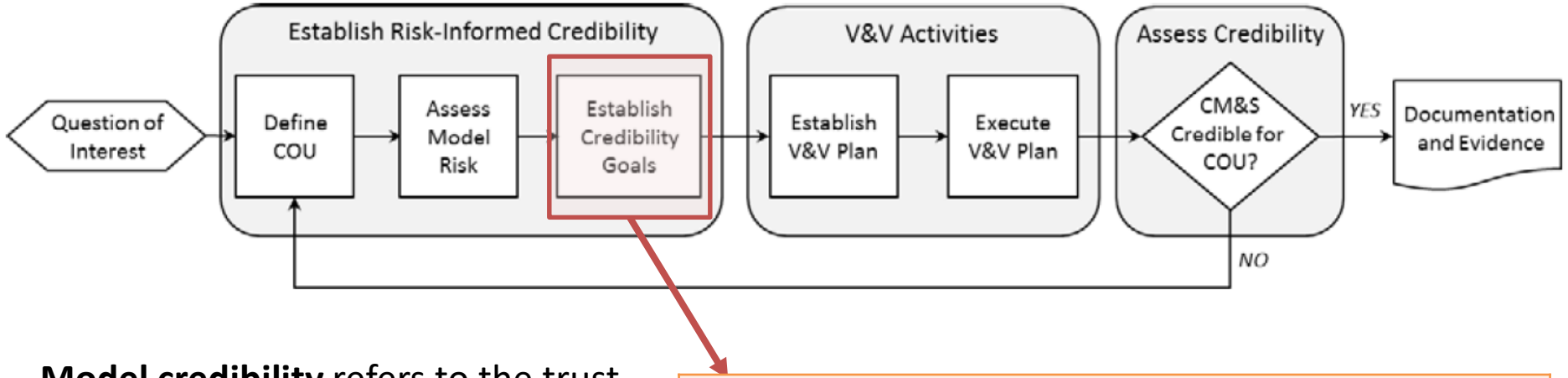


Model risk is the possibility that the model may lead to a false/incorrect conclusion about device performance, resulting in adverse outcomes.

- **Model influence** is the contribution of the computational model to the decision relative to other available evidence.

- **Decision consequence** is the significance of an adverse outcome resulting from an incorrect decision.

Model Credibility Factors



Model credibility refers to the trust in the predictive capability of the computational model for the COU.

Trust can be established through the collection of V&V evidence and by demonstrating the applicability of the V&V activities to support the use of the CM for the COU.

Credibility Factors														
Verification					Validation									Applicability
Code		Solution			Model				Comparator			Output Assessment		
Software Quality Assurance	Numerical Algorithm Verification	Discretization Error	Use Error	Numerical Solver Error	System Configuration	System Properties	Boundary Conditions	Governing Equations	Sample Characterization	Control Over Test Conditions	Measurement Uncertainty	Equivalency of input and output types	Rigor of Output Comparison	Relevance of the Quantities of Interest	Applicability to the Context of Use

Gradations for Credibility Factors

- Associated with each credibility factor is a gradation of activities that describes progressively increasing levels of investigation into each factor
- The gradations assist with planning and comparison of the activities that can impact model credibility
- Example from blood pump circulatory support model for rigor of output comparison
  1. Visual comparison concludes good agreement
  2. Comparison by measuring the difference between computational results and experimental data. Differences are less than 20%.
  3. Comparison by measuring the difference between computational results and experimental data. Differences are less than 10%.
  4. Comparison with uncertainty estimated and incorporated from the comparator or computational model. Differences between computational results and experimental data are less than 5%. Includes consideration of some uncertainty, but statistical distributions for uncertainty quantification are unknown.
  5. Comparison with uncertainties estimated and incorporated from both the comparator and the computational model, including comparison error. Differences between computational results and experimental data are less

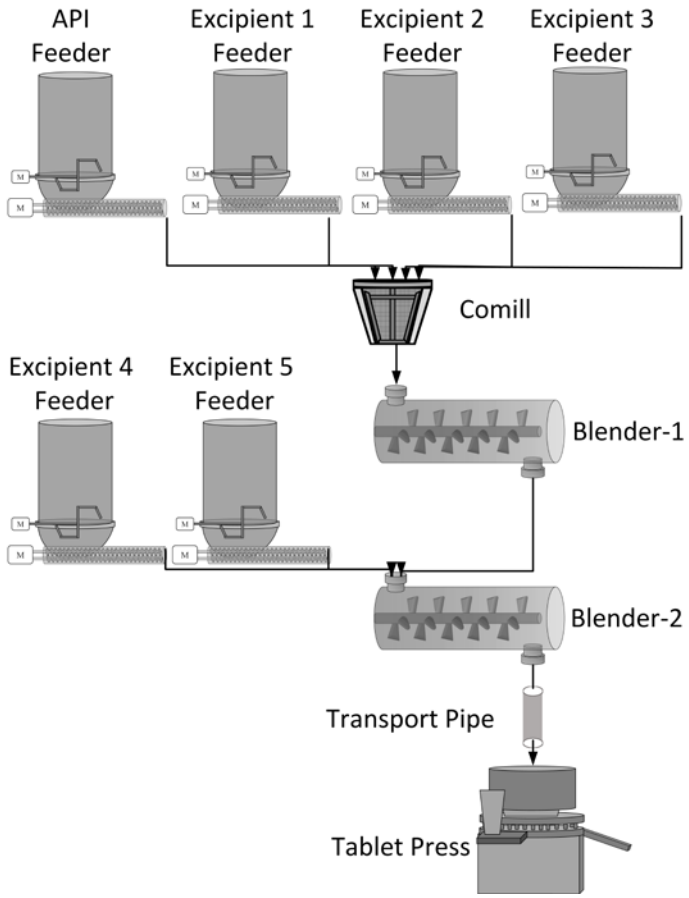
Upcoming ….

- ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products
  - Concept Paper – Content Q13
    - Key scientific approaches for CM concepts of system dynamics, monitoring frequency, detection and removal of non-conforming material, material traceability, *process models*, and *advanced process controls*
- ICH Q14 Analytical Procedure Development and Revision of Q2(R1) Analytical Validation
  - Concept Paper – Scope of Q2(R1) Revision
    - Validation principles that cover analytical use of spectroscopic or spectrometry data (e.g., NIR, Raman, NMR or MS) some of which often require *multivariate statistical analyses*

Case Studies

Case Study I: Monitoring of CDC Process

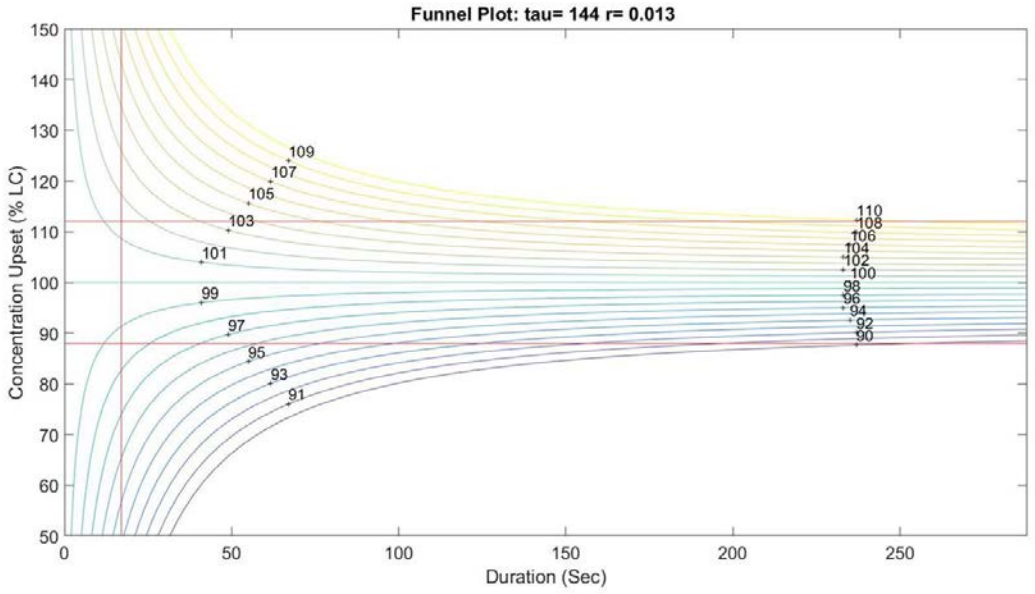
- Process dynamics can be characterized by the Residence Time Distribution (RTD)
- RTD is a probability distribution that describes the amount of time a mass or fluid element remains in a process
- Application of Residence time distribution (RTD) models
  - Predict blend and content variability based on feeding variability
  - Traceability and diversion of nonconforming material due to an unexpected even or disturbance
  - Support justification of excipient feeder limits



Example of CDC Process

Case Study I: Model Assessment using V&V 40 Framework

- Context of use is to monitor the concentration of the formulation components in the blend. In primary control strategy, API concentration is also measured by NIR and in the contingent strategy by stratified sampling of tablet cores.

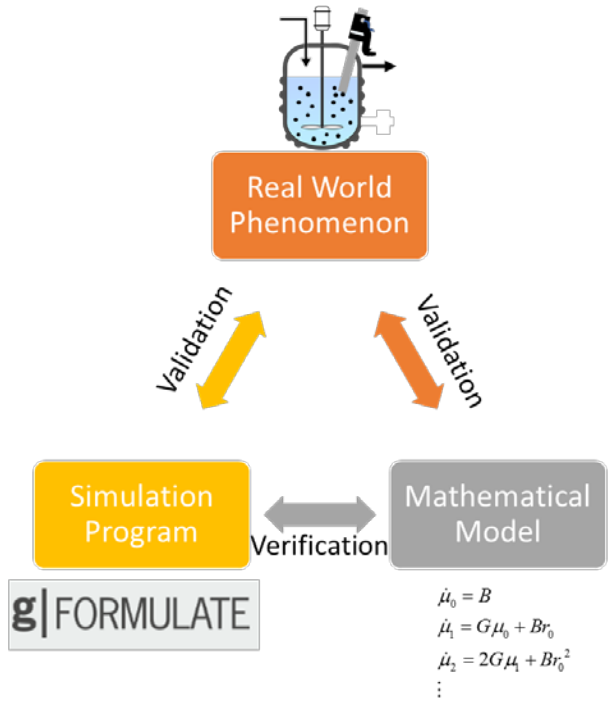


Data is illustrative and doesn't represent actual model output

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

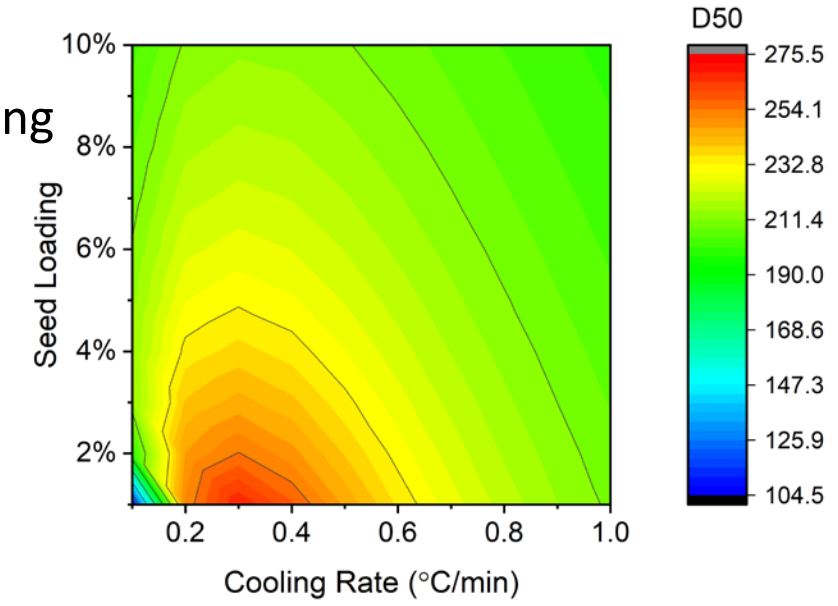
Case Study II Development and Validation of Crystallization Model

- Crystallization model development
  - Systematic experimental design to separate each phenomenon
  - Population balance modeling
  - Kinetic parameter estimation via model discrimination
  - Concentration and size prediction
- Model verification and validation
  - Risk-based approach
    - Understand the system → low risk
    - Establish design space and in-process control limits → medium risk
- Verification: verify numerical solution
- Validation: validate model prediction with experimental data
- Goal: Use model to find the design space for a target yield

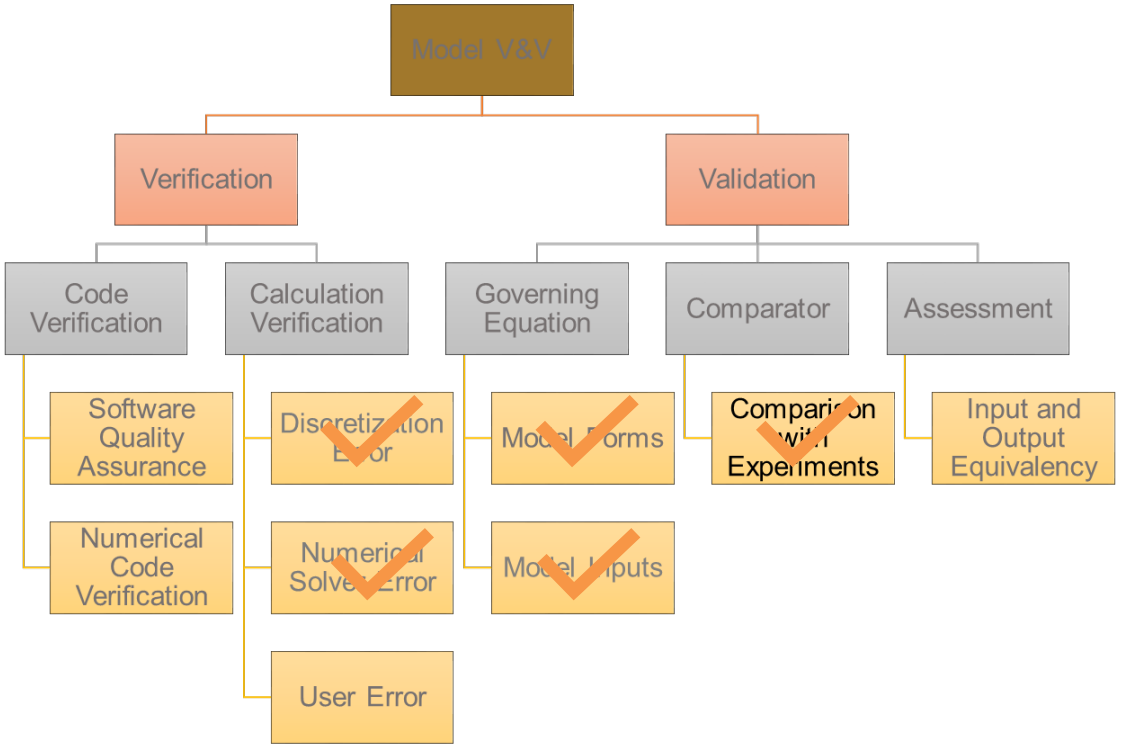


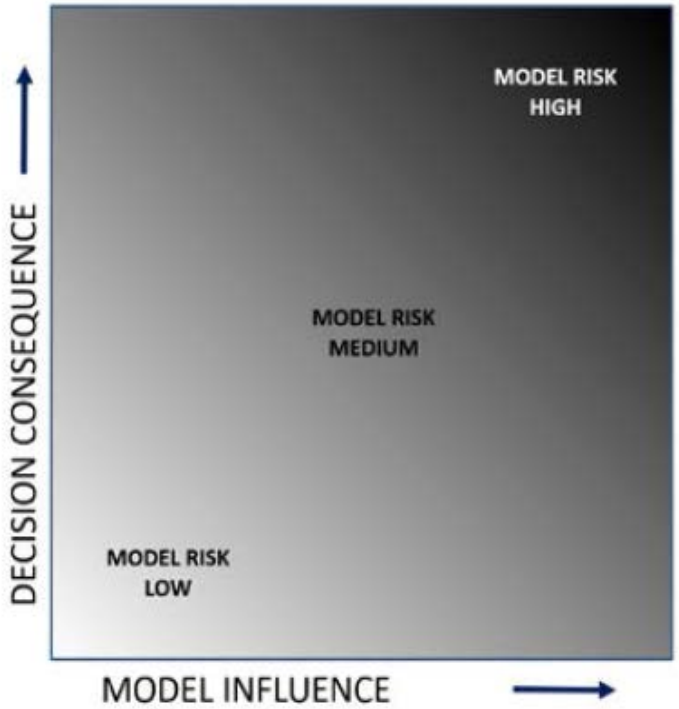
Application: Process Limit Identification

- PBM is developed, verified and validated
- Use PBM to find design space
  - Target response:D50
  - Parameters: initial concentration, cooling rate, seed size, seed loading, seed temperature
  - Identify 2 - 3 significant parameters by ANOVA
- Simulate in the space with the 2 – 3 parameters
  - E.X. Seed loading and Cooling Rate



Model Verification and Validation





Model Validation: Model Input Sensitivity

- Sensitivity study
  - Model outputs (concentration and size quantiles) to its inputs (kinetic parameters)
  - Monte-Carlo sampling technique: 100 samples randomly selected in their design space, i.e. confidence interval
- Process simulated 100 times at target conditions with randomly selected kinetic parameters

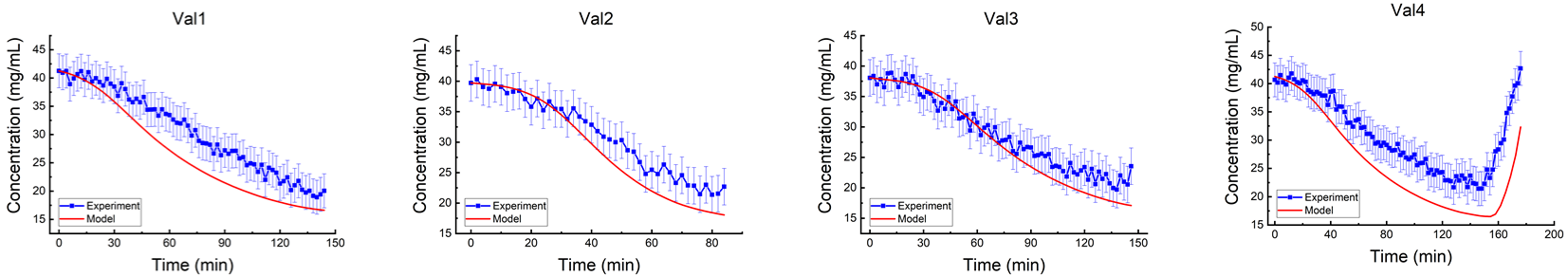
	C(mg/mL)	D10(µm)	D50(µm)	D90(µm)
µ	28.09	18.81	117.9	221.4
σ	0.021	0.019	0.404	0.370
CV	0.07%	0.10%	0.34%	0.17%

- Little to no sensitivity of concentration and size quantiles to kinetic parameters in their confidence interval range

Model Validation: Experimental Comparison

- Four external validation experiment: seeding T 35°C, T final 10°C
  1. 8% seed,125-212µm, 0.2°C/min
  2. 6% seed, 125-212µm, 0.4°C/min
  3. 10% seed, 75-212µm, 0.2°C/min
  4. Exp 3 + dissolution

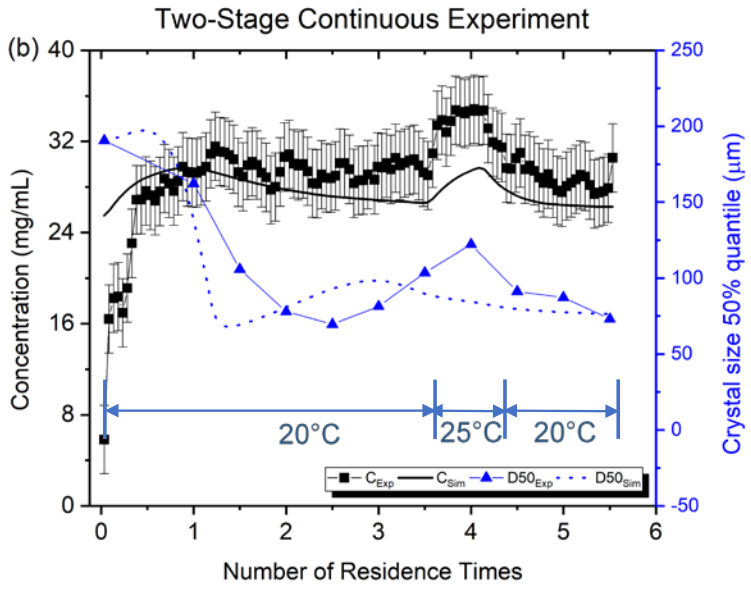
	Conc Mean Rel Err
Exp1	14.0%
Exp2	8.40%
Exp3	2.70%
Exp4	18.4%



	D10(µm)			D50(µm)			D90(µm)		
	Exp	**Model**	**Rel Err**	**Exp**	**Model**	**Rel Err**	**Exp**	**Model**	**Rel Err**
Val1	126.8	14.97	88.19%	190.7	206.7	8.39%	247.2	361.3	46.16%
Val2	133.2	21.58	83.80%	194.2	224.9	15.81%	243.9	384.1	57.48%
Val3	95.34	15.69	83.54%	159.4	203.9	27.92%	227.2	339.7	49.52%

Applicability

- Applicability is the relevance of the validation activities to support the use of the computational model for a context of use



Comparison of experimental and simulated dynamic concentration, and D50 for a two stage continuous crystallization process

Opportunities

- Develop end to end case studies for different model types and different model impact level
  - Publish case studies in special issue?
  - Hold workshop to discuss?
- General principles apply to all models but different model types (mechanistic/empirical) specific considerations
- Case studies could be used to stress test proposed gradients for credibility factors

Lifecycle

Maintenance Considerations for Process Models

- Selection of reporting category for post approval change depends on potential for the change to have an adverse effect on product quality (CFR 314.70)
- Establish approach to determine reporting category of changes to models over product lifecycle.
- Can leverage **comparability protocols/PACMP** for alternate reporting categories

		Potential impact of the change on model's performance		
		Low	Medium	High
Potential impact of the change on product quality	Low			
	High			

Identification of Established Conditions for Performance Control Strategy Including Models

- Model enabled performance based control strategy approach
- Hypothetical powder Blending Unit Operation Example

	Parameter	Acceptable ranges and reporting categories		
		Parameter Based Approach	Enhanced Approach	Performance Based Approach
Input Materials	API PSD	20-50µm (PA)	5-200µm (NM)	5-200µm (NM)
	API Moisture	<1.0% (NL)	<1.0% (NL)	<1.0% (NL)
	Excipients #1-3 Specifications	Pharmacopoeial	Pharmacopoeial	Pharmacopoeial
Equipment Parameters	Equipment Type	Diffusion blender (PA)	Diffusion blender (NM)	Diffusion blender (NM)
	Scale	200kg (NM)	200kg (NL)	200-600kg (NL)
	Blend Speed	20rpm CPP (NM)	10-20rpm KPP (NL)	15 rpm (NR)
	Blend Time	20 min CPP (NM)	15-25min KPP (NL)	20 minutes (NR)
Online Performance Measure	Homogeneity Method	Not tested	Not tested	NIR online analyzer (PA)
	Homogeneity	Not tested	Not tested	<5% RSD IPC (NM)

In performance based approach process parameters are not established conditions

Feedback control approach and tuning not established conditions

Measurement of process performance and acceptance criteria are established conditions though

Q12 Annex Step 2

Concluding Thoughts

- Regulatory experience with process modeling is evolving
- Emerging technologies are a potential driving force for utilization of process models throughout a product lifecycle
- OTR utilizing process models to support regulatory science, product quality assessment, and policy related to advanced manufacturing
- Model validation and maintenance activities should be fit for purpose

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