U.S. FOOD & DRUG ADMINISTRATION

Perspective on the Validation of Computational Models for Establishing Control Strategies

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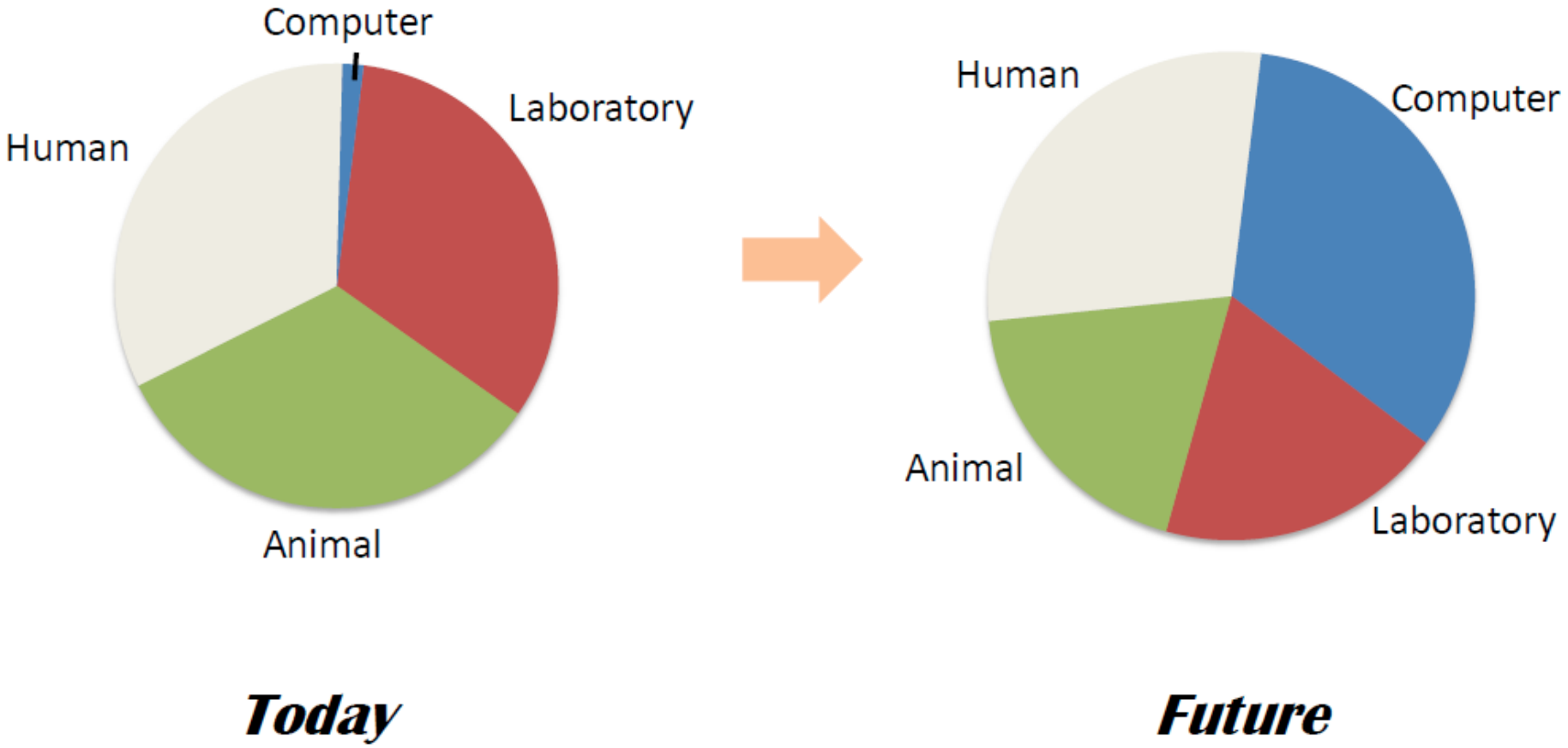
Disclaimer

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

Sources of Scientific Evidence



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

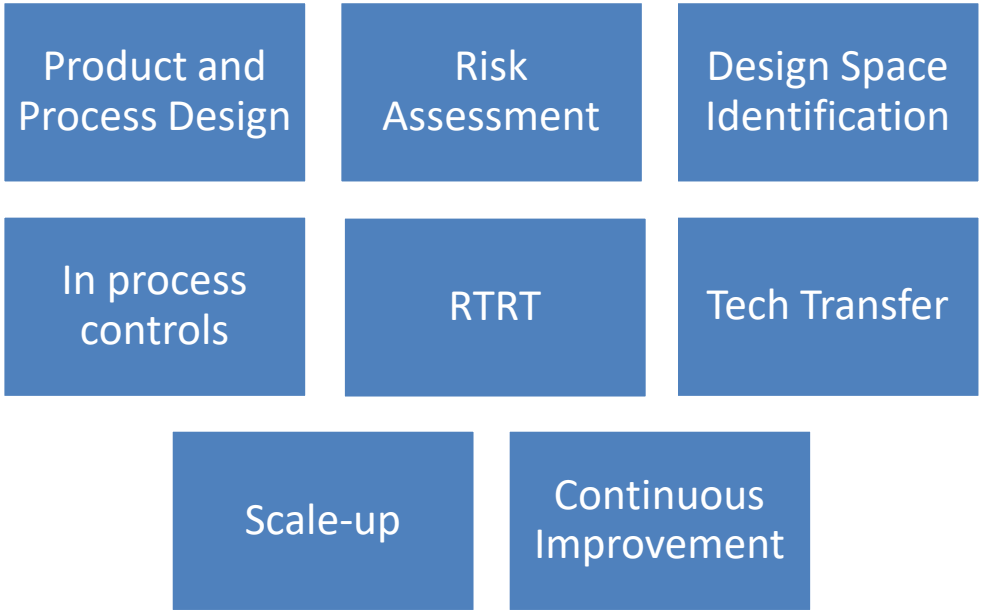
FDA Modeling and Simulation (M&S) Working Group

- 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

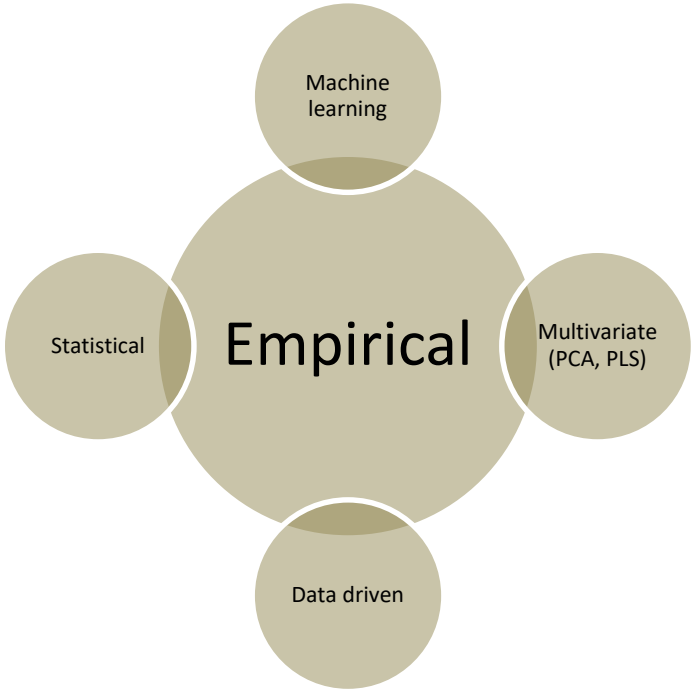
Chemical	Mechanistic	Statistical	Physics	Big Data	Risk Assessment
• QSAR • Chemometrics • Quality by Design • Molecular docking	• PK/ADME • PK/PD • Lumped parameter • Systems modeling	• Stochastic • Bayesian & adaptive • Monte Carlo • Population modeling • Social network analysis	• Acoustics • Electromagnetics • 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?

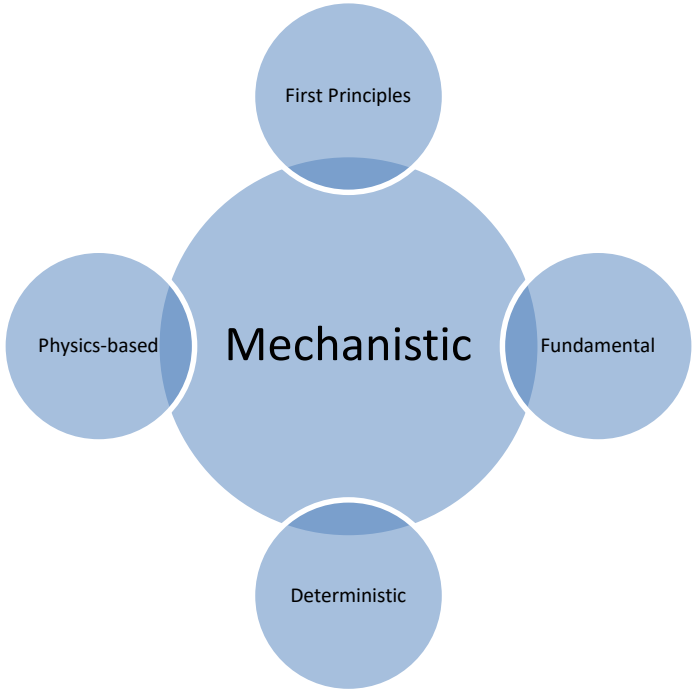
- In Quality by Design framework, mathematical models can be utilized at every stage of product development and manufacturing
- Predictive models have been implemented for developing and controlling processes and have appeared in regulatory submissions
  - Dissolution models for release
  - Multivariate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



Modeling Terminology



Learn to recognize relationships by experience



Understand scientific basis for the relationship between variables

Hybrids

Modeling Benefits and Challenges

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

Advantages

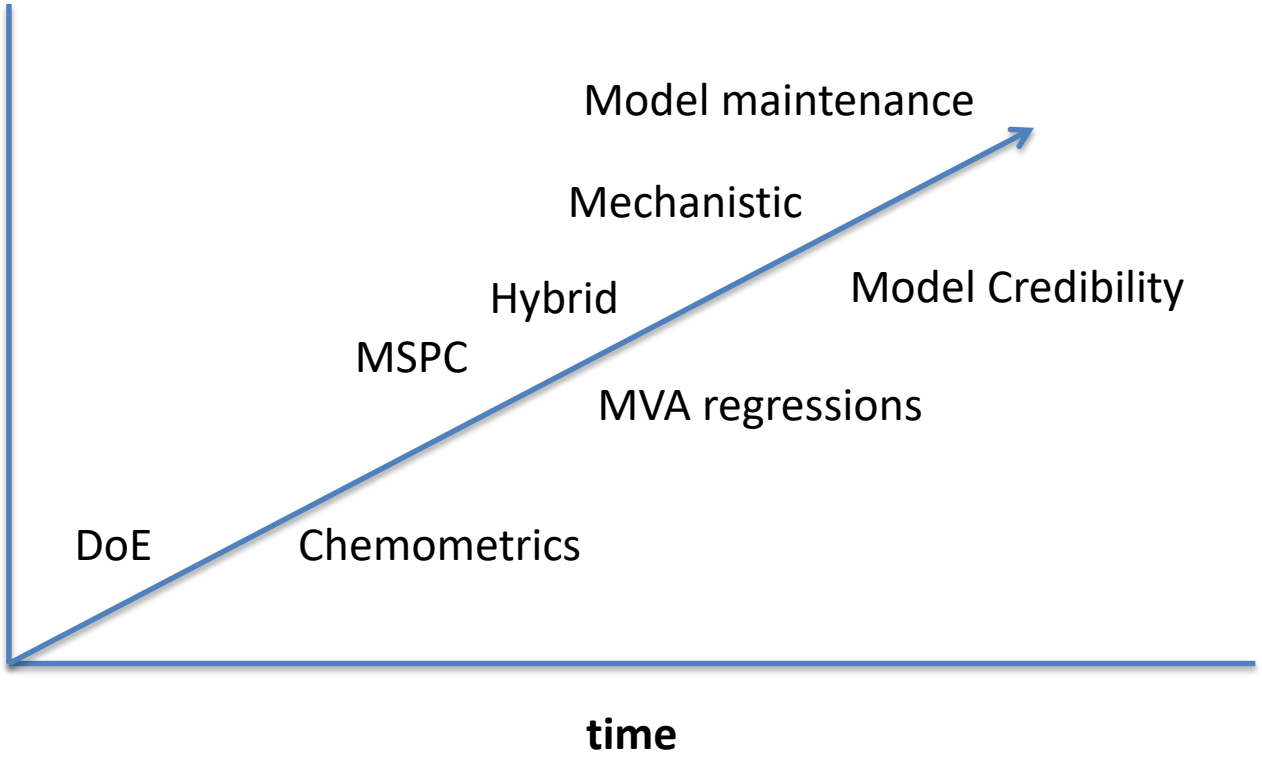
1. Repositories of data and information: reduction of data to an equation
2. Establish input and output relationships (CPPs to CQAs)
3. Extract information from large data sets
4. Improve process design and performance
5. Risk assessment of changes prior to implementation
6. Facilitate implementation 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

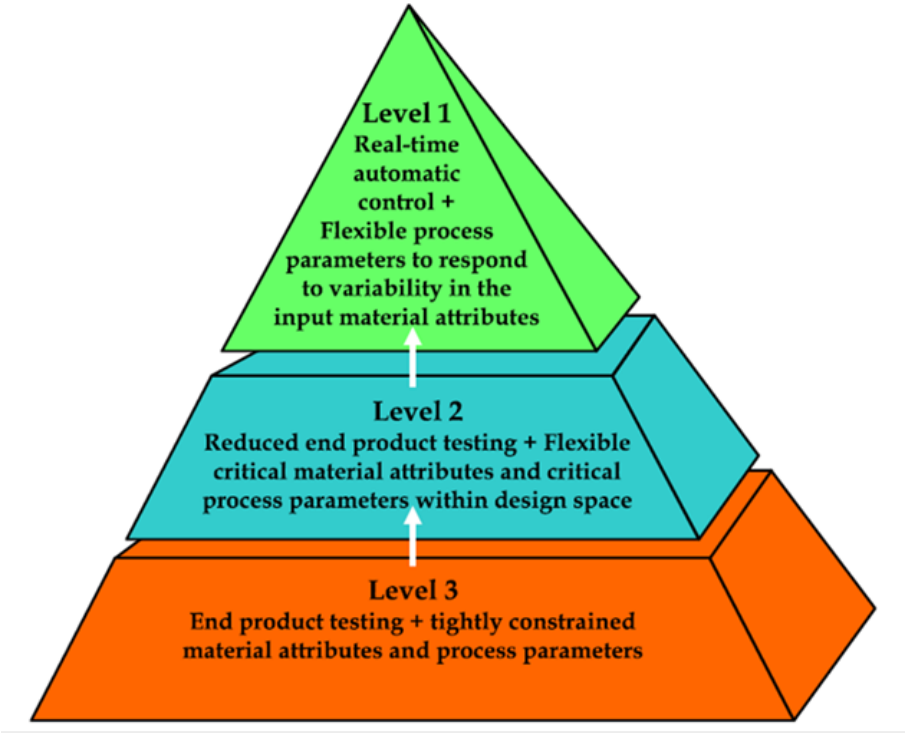
Evolution of Process Modeling: Regulatory Perspective

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



Advanced Manufacturing as 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.)

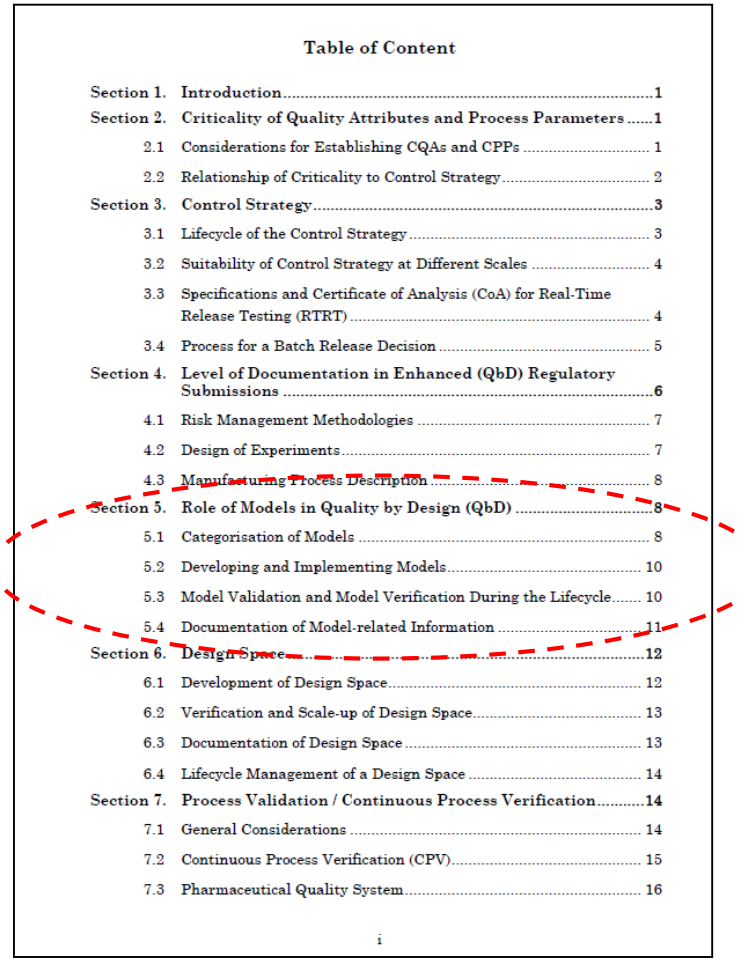


Lee S. *et. al.* J Pharm Innov. **2015** DOI 10.1007/s

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

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

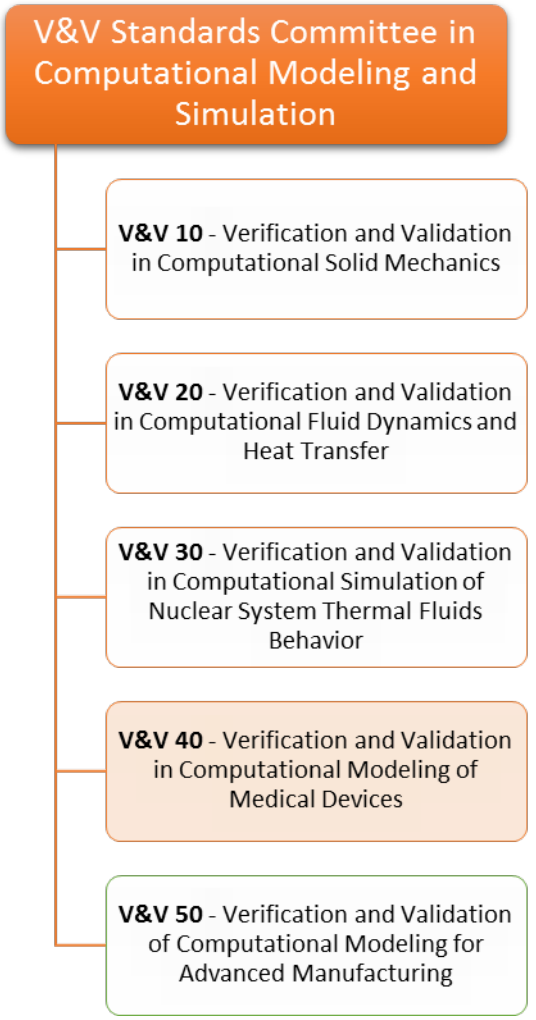
- Rules developed by a multidisciplinary committee facilitated by the Interagency Modeling and Analysis Group[1]
  1. Define context clearly
  2. Use appropriate data
  3. Evaluate within context
  4. List limitations explicitly
  5. Use version control
  6. Document adequately
  7. Disseminate broadly
  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

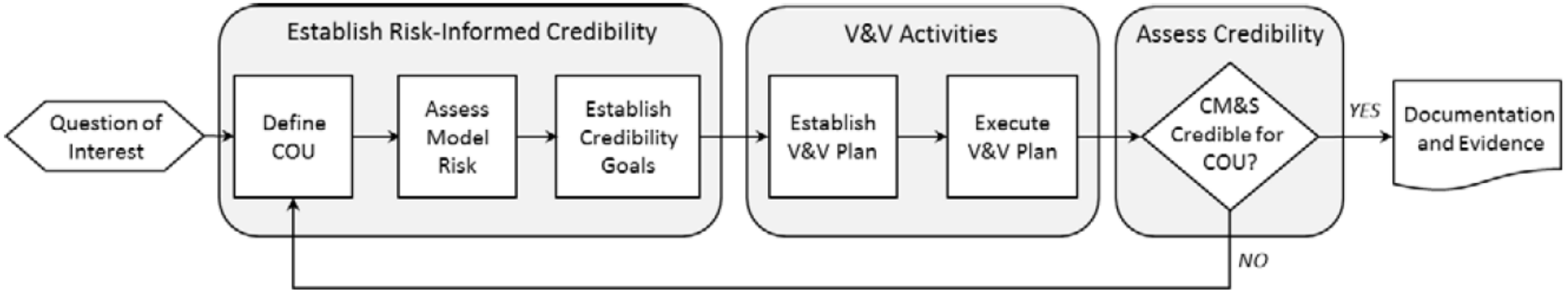
ASME Verification and Validation (V&V) 40

- 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. Validation concepts can also be applied to empirical models

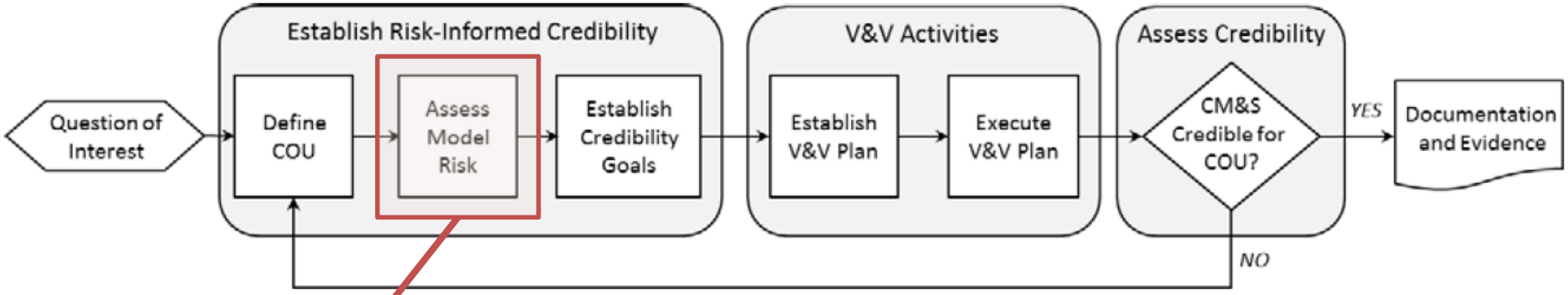
Risk-Informed Credibility Assessment Framework

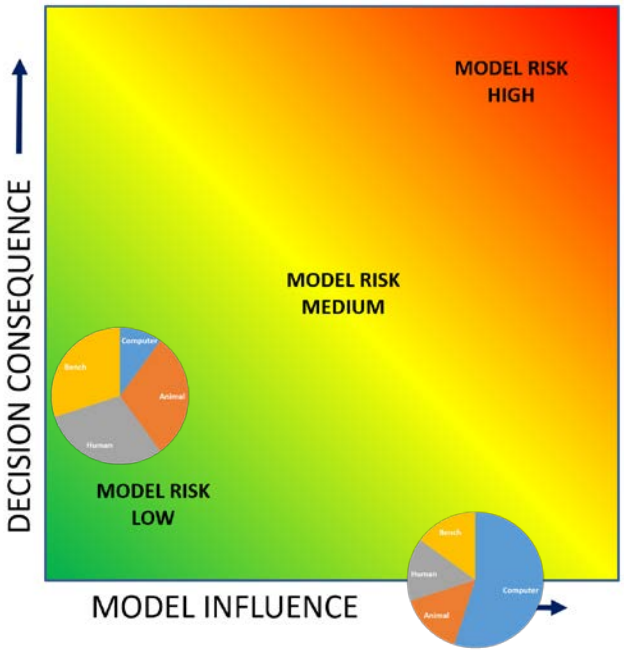


The V&V40 guide outlines a process for making risk-informed determinations as to whether M&S is credible for decision-making for a specified context of use.

- 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



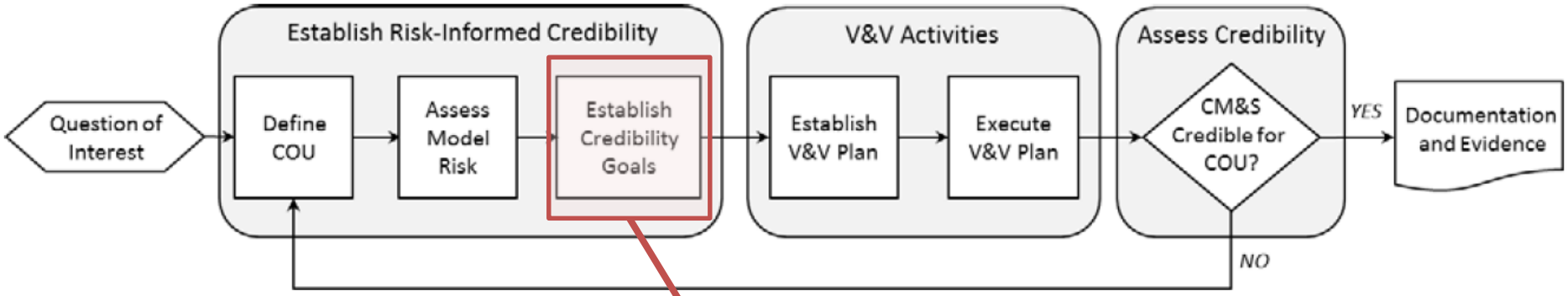


Model risk is the possibility that the model may lead to a false/incorrect conclusion about device performance, resulting in adverse outcomes.

- 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

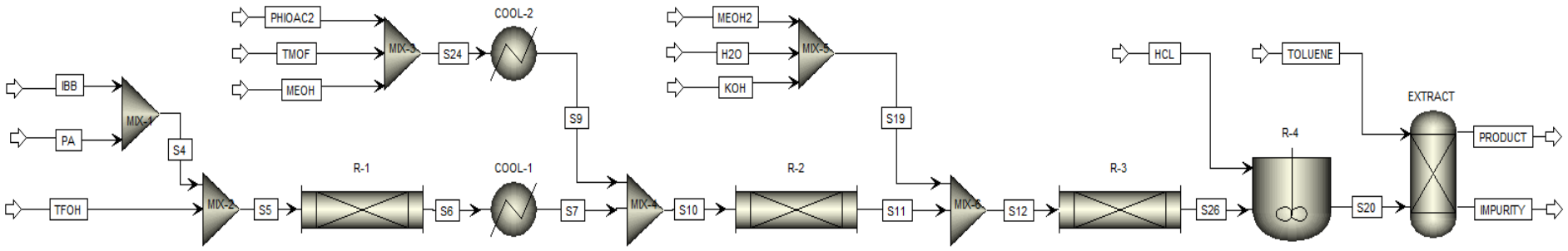
Gradations for Credibility Factors

- 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

Case Study I: Design Space for a Continuous Drug Substance Process

- Process understanding for flow reactors includes reactions kinetics, mixing, heat and mass transfer which can all be interdependent
- Continuous telescoped reaction processes have a large number of interacting parameters which can be time consuming to study using a DoE approach
- Cast study from submission
  - Measured reaction kinetics for major and minor reaction pathways
  - Heat balance for the reactors, based on measured reaction calorimetry, was included in the model
  - System is well mixed so assumed plug flow behavior

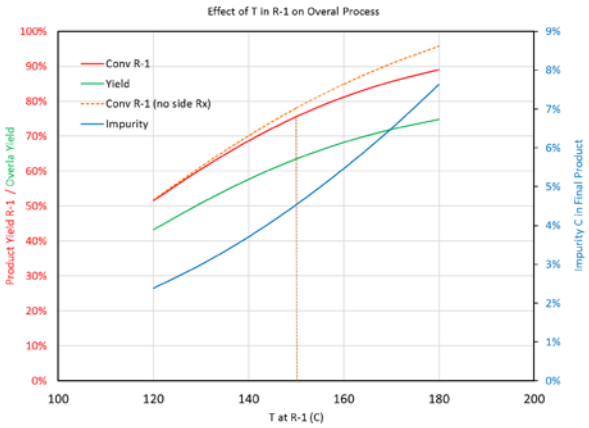
Process flow diagram of continuous ibuprofen manufacturing with flow chemistry

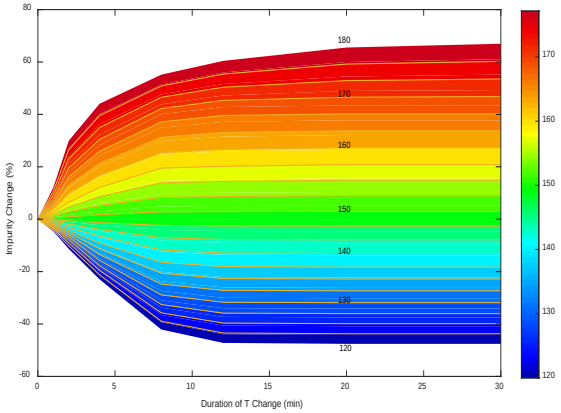


Case Study I: Model Assessment using V&V 40 Framework

Context of use is to define parameter ranges for a design space based on predicted levels of impurities at the end of the synthesis process. Design space ranges were experimentally confirmed at the most forcing combination of process parameter settings for process generated impurities that present the highest potential risk to drug substance quality.

Impact of temperature on impurity formation



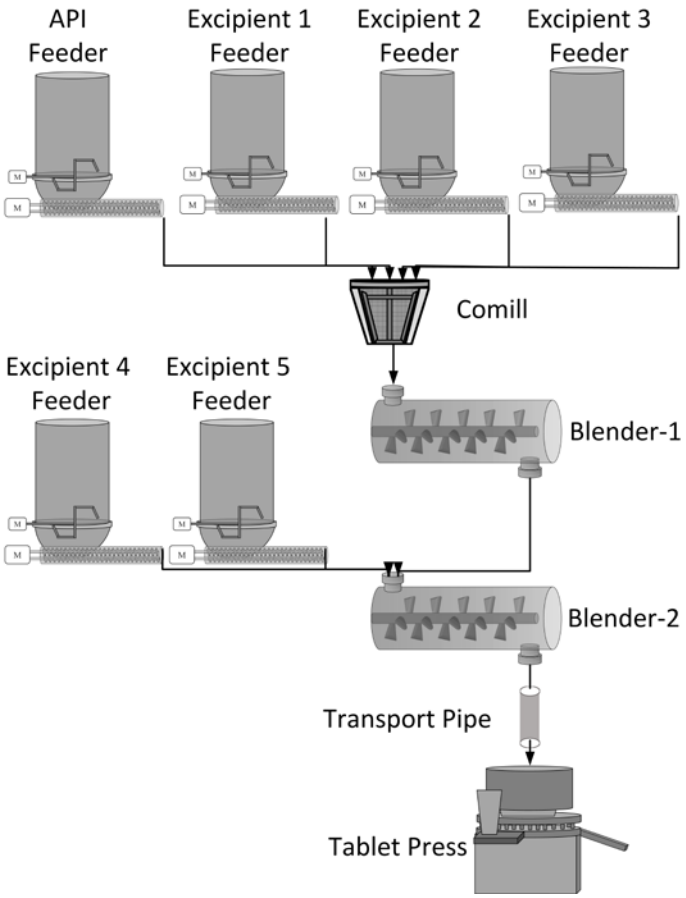


Data from a similar system model for the continuous manufacturing of ibuprofen

Credibility Factor	Activities
Code Verification	Utilized commercial software
Calculation Verification	Not provided
Governing equations	Mechanistic reaction pathways were challenged with alternative mechanisms
Parameters	Sensitivity analysis of conducted on process parameters
Comparator	Sixteen runs with parameter setting intended to force impurity formation
Validation Assessment	Confirmed that both predicted and measured impurity concentration were below targeted limited set by purging studies
Applicability	Validation activities were aligned with the proposed design space: model runs consisted 537 run DoE

Case Study II: Monitoring of CDC Process

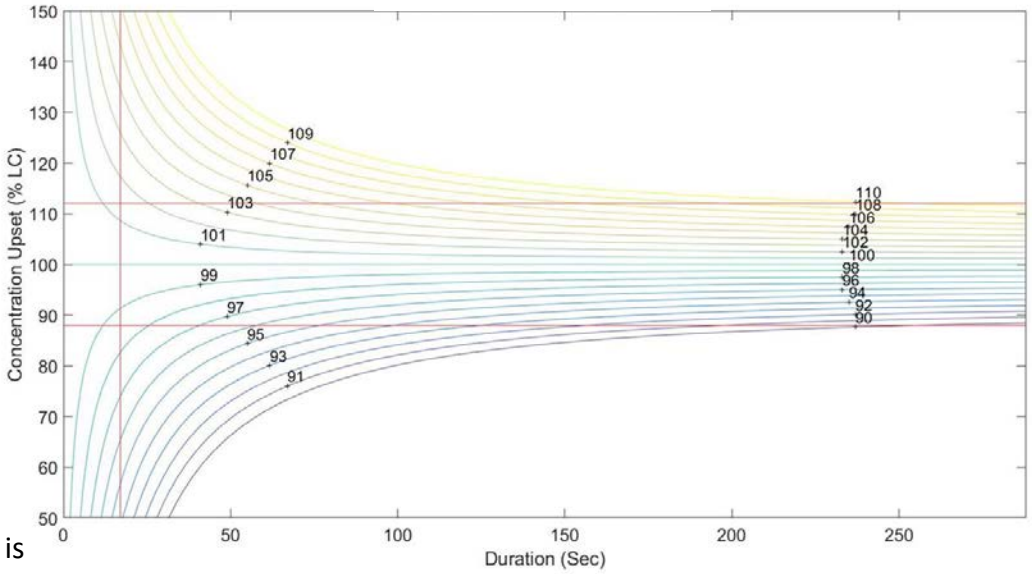
- Process dynamics can be characterized by the Residence Time Distribution (RTD)
- RTD is a probability distribution that describes the amount of time a mass or fluid element remains in a process
- Application of Residence time distribution (RTD) models
  - Predict blend and content variability based 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 II: 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.

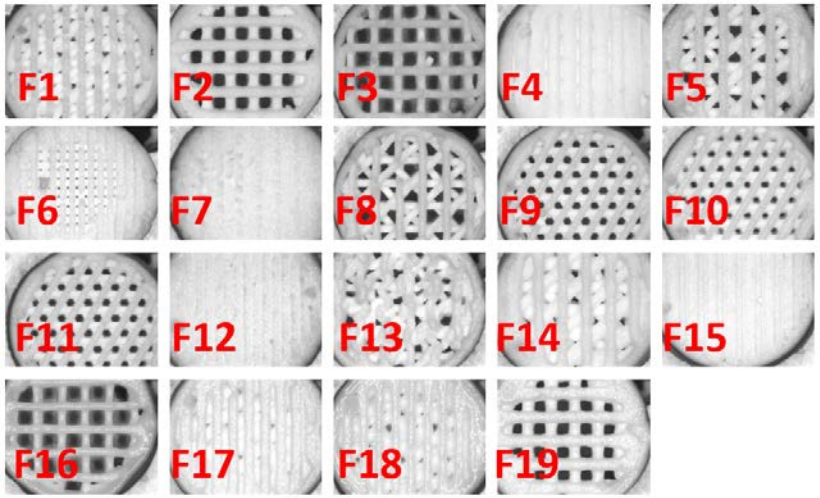


Data is illustrative and doesn't represent actual model output

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

Modeling for Patient Centric Medicine

Pressure assisted micro-extrusion 3D printing

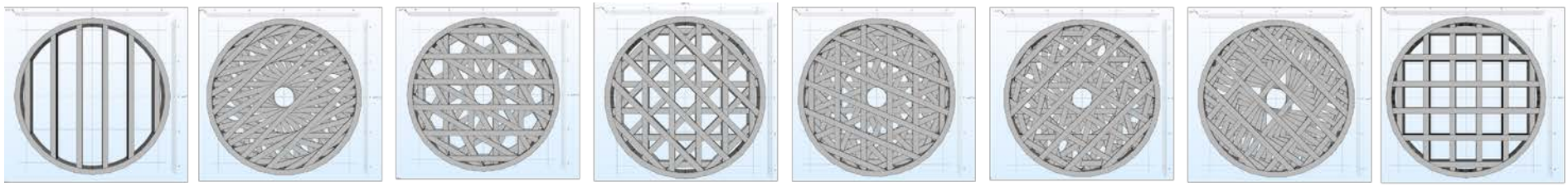


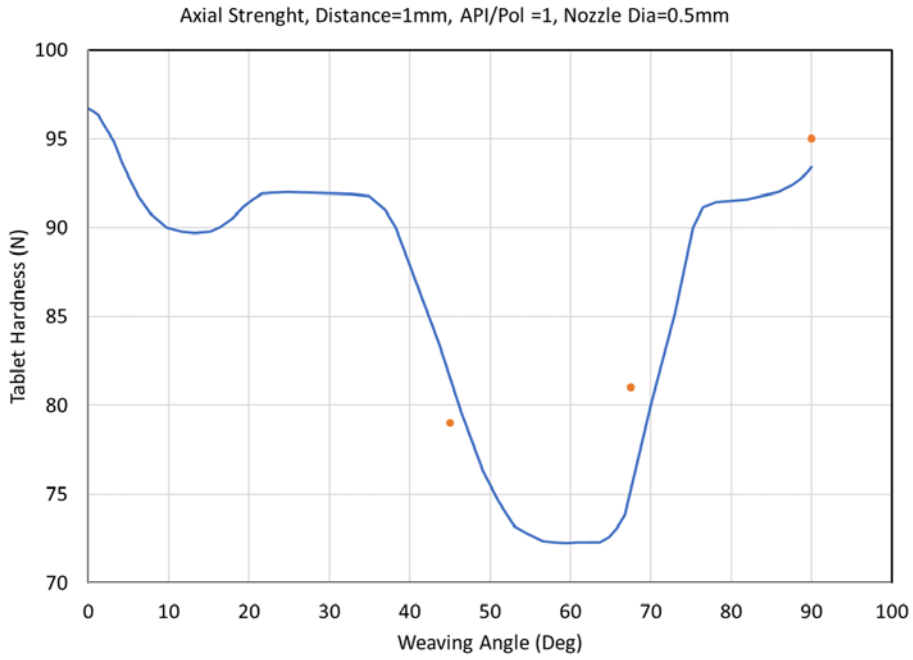
- Printing semisolids are released from print head under pneumatic pressure
- Material can be preheated to produce the desired viscosity for extrusion.
- Layers (multiple print heads possible) fuse or bond followed by curing or drying
- Powder loaded semisolids pastes can be used for printing oral drug products.

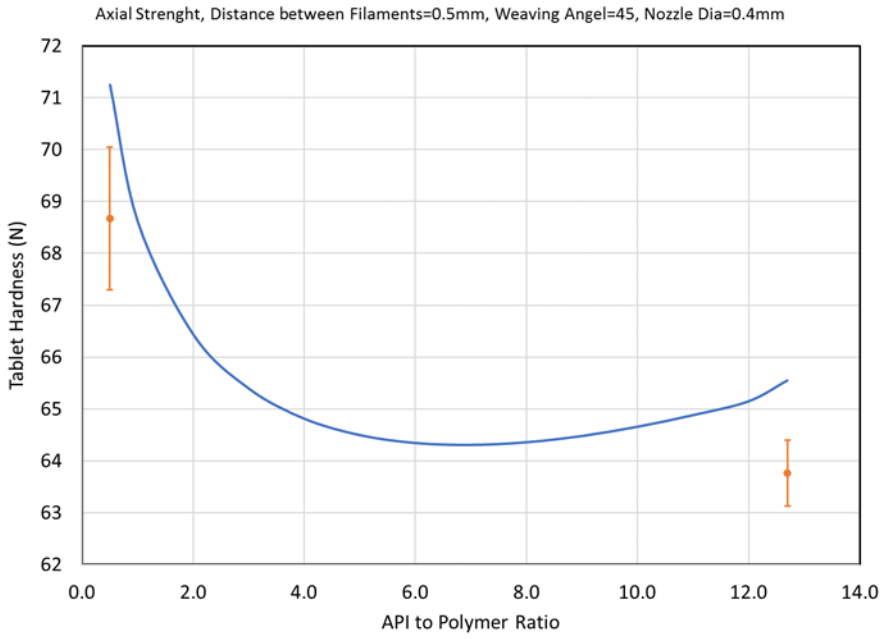
Int J Pharm. 2019 Jan 30;555:109-123.
Int J Pharm. 2019 Jan 10;554:292-301.

Computational Modeling of 3D Printed Tablet Quality Attributes

Modeling physical properties as a function of geometry and formulation

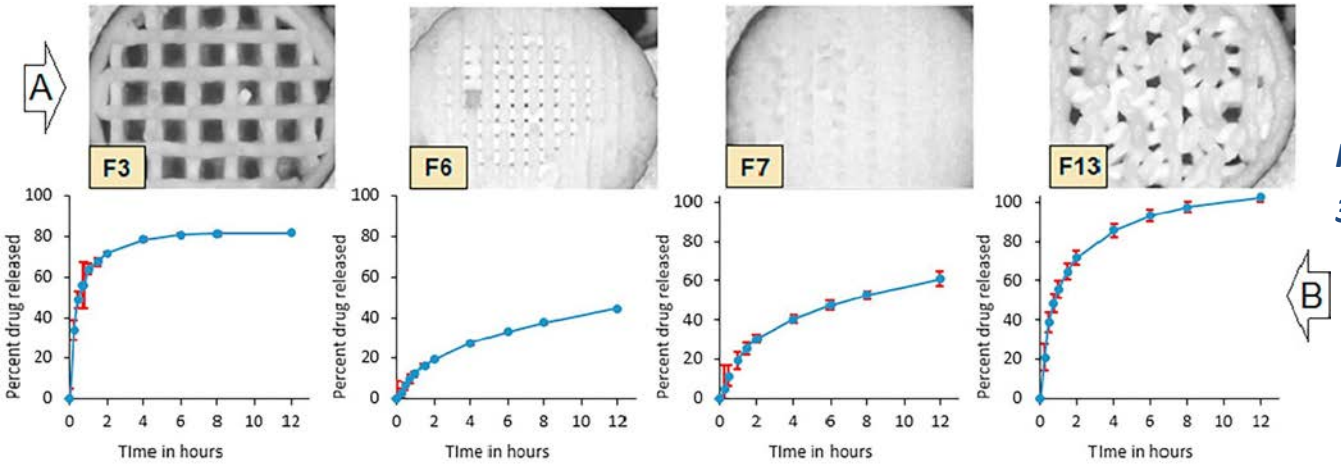






Computational Modeling of 3D Printed Tablet Quality Attributes

Next phase is exploring whether we can predict dissolution behavior for these tablets



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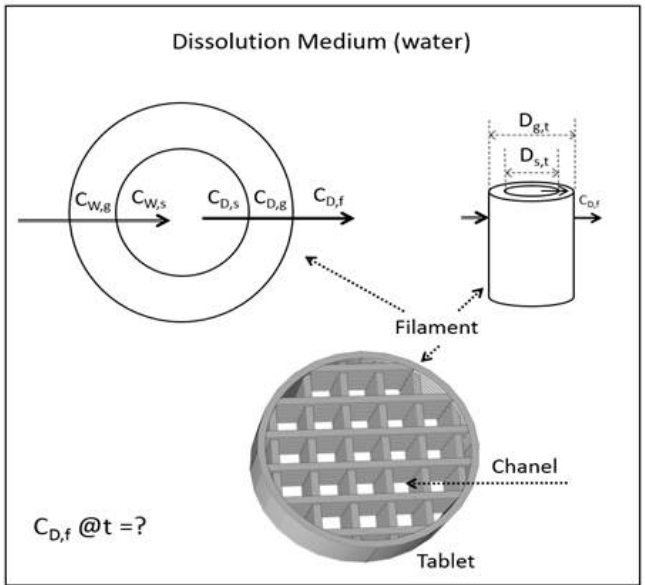

$$\frac{\partial C_i}{\partial t} = \nabla\left(Dif_{i,t}\nabla C_i\right)$$

Diffusion, water in or drug out

$$Dif_t = Dif_{eq}\, exp\left[-\beta\left(1 - \frac{C_{i,t}}{C_{1,eq}}\right)\right]$$

Concentration dependent diffusion, water or drug

$$\frac{\partial D_r}{\partial t} = \frac{\partial C_{w,i}}{\partial t} + Dif_{i,t}\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial D_r}{\partial r}\right) - \frac{1}{r^2}D_r\right]$$

Swelling

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
- Verification and validation activities for models used to support controls strategies should be fit for purpose
- ASME V&V 40 standard, along with current regulatory guidance, can be useful for developing a model verification and validation plan

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