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MiniCase study:
Implementation of Novel Strategies and Novel Technologies for Acceleration of IND and BLA Submissions

CASSS WCBP – 2023

Stephane Avella

Regulatory CMC Biologics

Merck & Co., Inc., Rahway, NJ, USA

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Innovative 2-Stage Approach to Comparability Assessment for Acceleration of IND/CTA Submissions

Process and Analytical Comparability Assessment and Testing Strategy

DS Manufacturing Process/Site	Analytical Comparability				Process Comparability
	Release	Stability	Extended Characterization	Forced Degradation	
Clinical site Pre-change	X	X	X	---	X
	X	X	X	X[1]	X
	X	X	X	X[1]	X
	X	---	X	---	X
Commercial site Post-change	Initial stage Assessment-Post Change Lots				
	X	X	X	X[1]	X
	Final Stage Comparability Assessment -Post Change Lots				
	X	X	X	---	X
	X	X	X	---	X
	X	X	X	---	X

[1]Forced degradation performed for Initial Stage Assessment only

Initial Stage Assessment

- **Amendment 1**: After Health Authority review & approval of data from 1 post-change DS batch meeting the comparability acceptance criteria

  → Drug product from that single post-change DS batch will be released for clinical use

Final Stage Assessment

- **Amendment 2**: After Health Authority review & approval of data from 3 post-change DS batches meeting the comparability acceptance criteria

  → All subsequent drug products from post-change DS batches can be released for clinical use

- **2-stage approach to comparability assessment enables rapid introduction/resupply of a single post-change material meeting product quality into late-stage Phase 3 clinical studies**
- **Approach was endorsed by FDA Type C Written Responses and EU Scientific Advice**

Mini Case Study

New Strategies for Acceleration of IND and BLA Submissions

Mechanistic Modeling

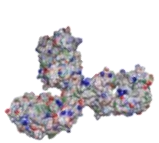
BDB
Bioprocess Development Biologicals

Boehringer Ingelheim

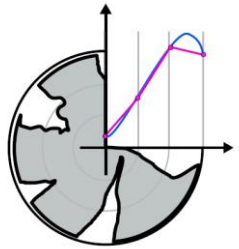
FDA U.S. FOOD & DRUG ADMINISTRATION

Boehringer Ingelheim

Mechanistic model for preparative chromatography



Interfacial mass transfer between the bulk fluid phase and the particle phases

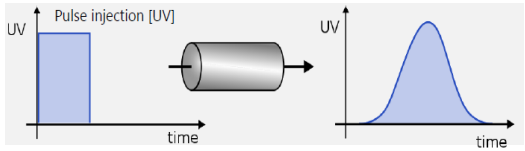


Convective transport

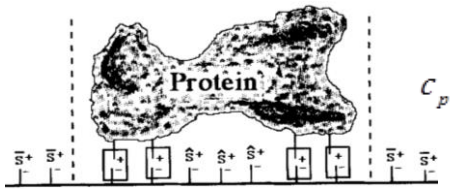
$$\frac{\partial c}{\partial t}(x,t) = -\frac{u(t)}{\varepsilon_{col}}\frac{\partial c}{\partial x}(x,t) + D_{ax}\frac{\partial^2 c}{\partial x^2}(x,t) - \frac{1-\varepsilon_{col}}{\varepsilon_{col}}\left(\varepsilon_{part}\frac{\partial c}{\partial t} + \left(1-\varepsilon_{part}\right)\frac{\partial q}{\partial t}(x,t)\right)$$

Accumulation in the liquid phase

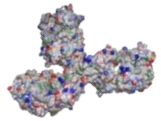
Axial dispersion



Adsorption isotherm, e.g. steric mass action (SMA) isotherm for IEC



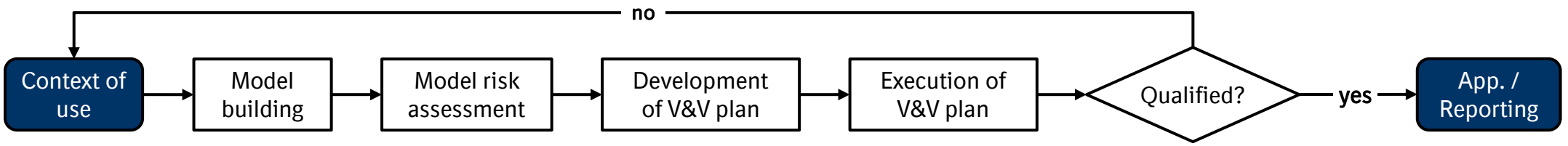
$$c_p = \left(\frac{q_p}{K_{eq}}\right)\left(\frac{c_s z_s}{\Lambda - (\sigma+\nu)q_p}\right)^{\nu}$$



For modeling, we need to have a plan…

- What do you want to do with your models?
- What do you want to predict?
- What problems you want to solve?
- Where and how will your models be implemented to make what type of decisions…

Risk-Based Model Verification & Validation Workflow

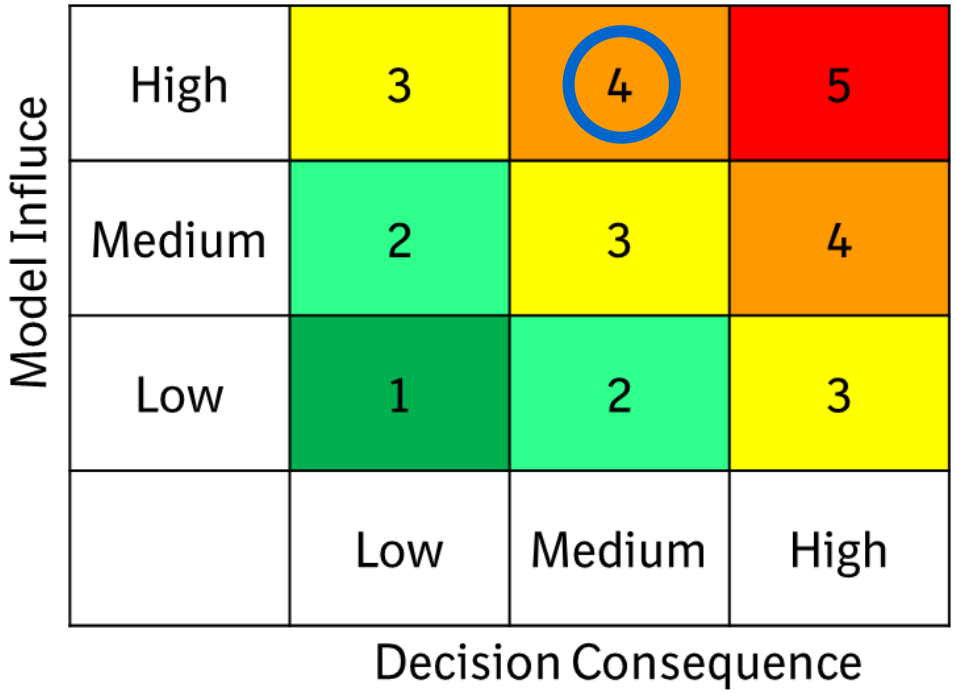


Established framework is influenced by:

- ASME Verification and Validation (V&V) 40 standard
- FDA draft guidance: FDA-2021-D-0980
- ICH points to consider document

Risk of Model Based Data

- Mechanistic Model calibrated and validated
- Execute PCS for single unit operation with no wet lab data.
- Model risk: medium
  - Model Influence: high because process control for this CEX was entirely based on model data.
  - Decision Consequence: medium because final batch release testing carried out to ensures product quality.



Strategy to Implementation

CEX model calibration, validation, and application – setting the industrial standard

- Publications on model calibration/validation strategy
- First *in silico* PCS executed in addition to wet lab PCS
- **Interaction with FDA's ETT in March 2021**
- Model included in BLA (S.2.6)

Model based decisions in development

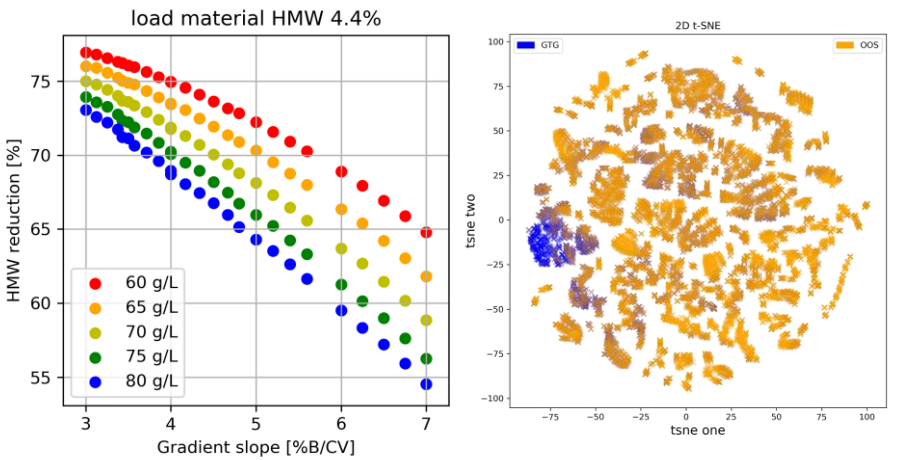
- CEX root cause investigation of 12k Tech Runs
- Design space determination method based on machine learning

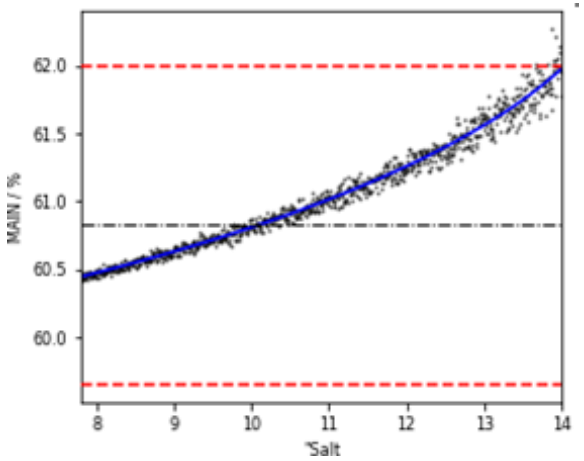
CEX model benefit gained in the field application

- Optimization of linear gradient elution entirely performed *in silico*
- Process successfully consolidated with model predictions confirmed

PCS for CEX step entirely based on mechanistic model

- PARs defined by *in silico* PCS will be part of control strategy
- **Second interaction with FDA's ETT in May 2022**





Mechanistic model for preparative chromatography

Once a mechanistic model is validated as a digital twin of the manufacturing process, it can be used for in silico process characterization.