AI Powered End-to-End Process Digital Twins: Applications, Benefits and Challenges

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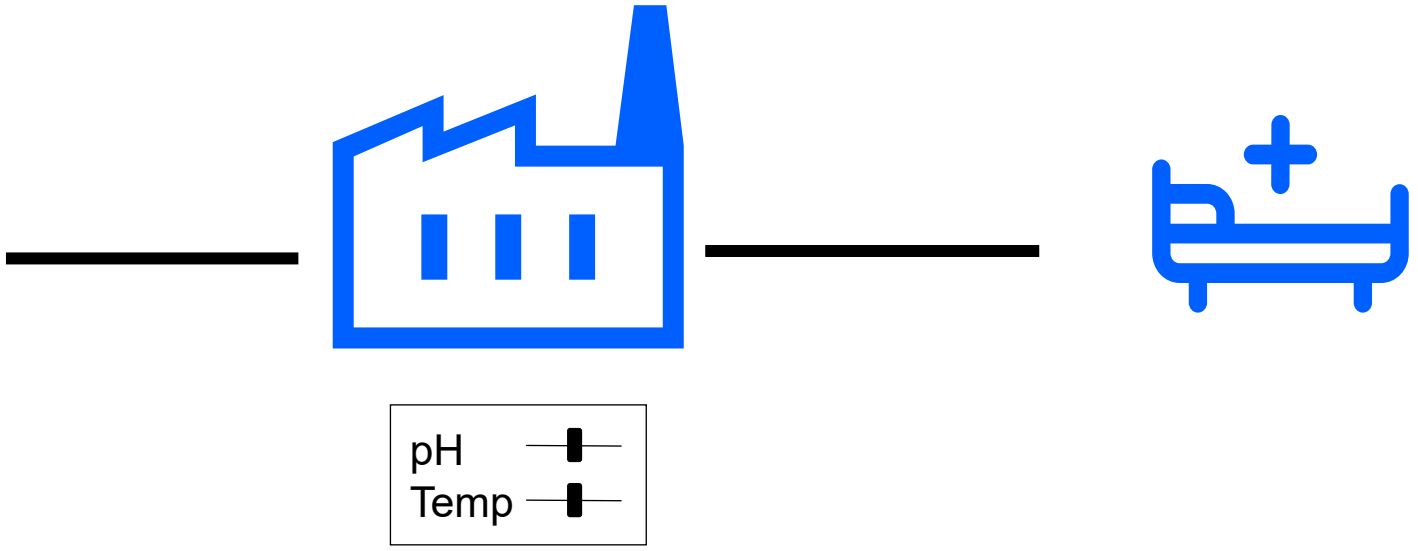
25th of June 2026, CMC Strategy Forum 2026

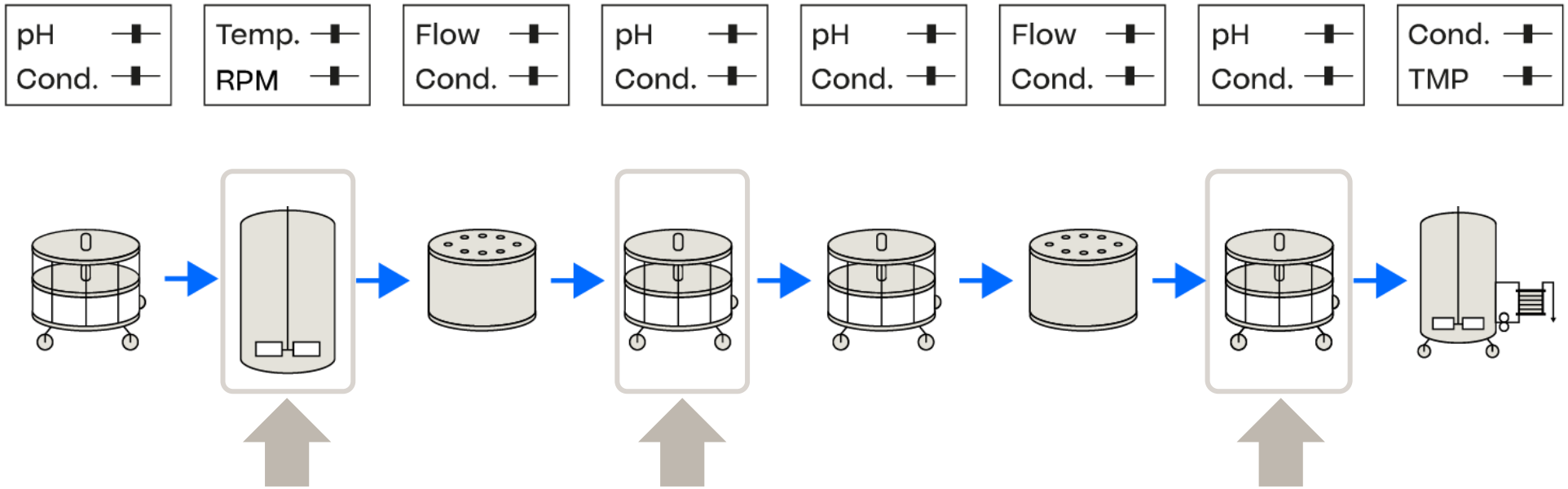
Why Process Digital Twins?



Why Process Digital Twins?

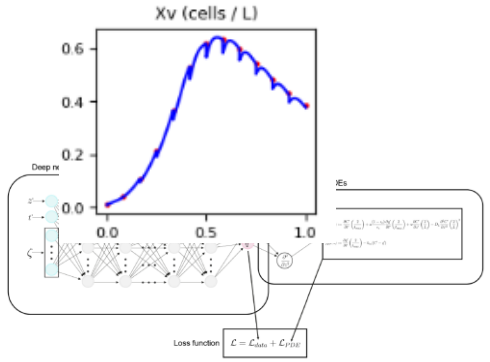
- Reduction of OOS results
- Increased space-time yield
- Increased reproducability
- Sustainability
- Decrease cost of goods

End-to-End Process Models as a Framework

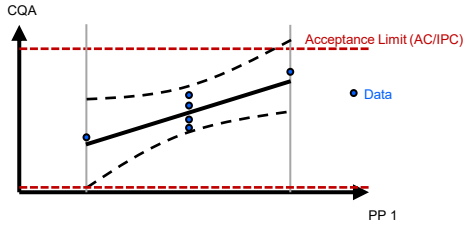


Product
Amount
CQA 1
CQA 2
…
CQA 15

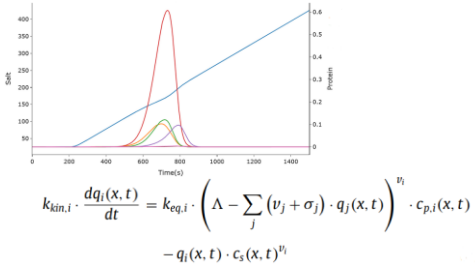
Hybrid and AI Models



Data driven / statistical models

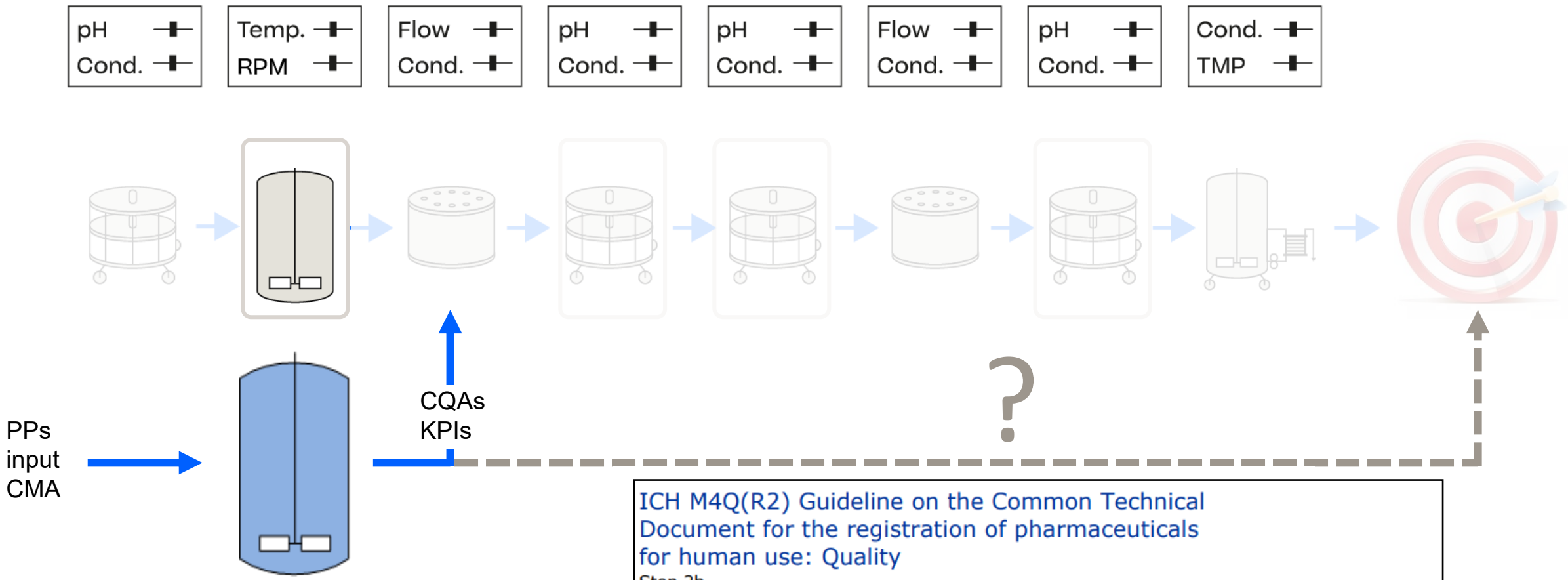


Mechanistic Models



$$k_{kin,i} \cdot \frac{dq_i(x,t)}{dt} = k_{eq,i} \cdot \left(\Lambda - \sum_j (\nu_j + \sigma_j) \cdot q_j(x,t)\right)^{\nu_i} \cdot c_{p,i}(x,t) - q_i(x,t) \cdot c_s(x,t)^{\nu_i}$$

End-to-End Process Models as a Framework



ICH M4Q(R2) Guideline on the Common Technical Document for the registration of pharmaceuticals for human use: Quality

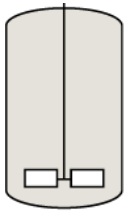
Step 2b

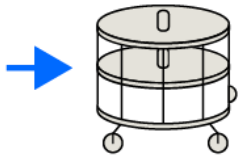
2.3.2.3 Overall Control Strategy Representation

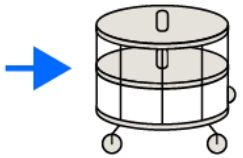
The OCS is a holistic and integrated approach encompassing considerations from the CQAs to the end-to-end controls, describing how the individual control strategies interact to ensure product quality (ICH Q6A/Q6B, Q8, Q9, Q10, and Q11). A representation, such as a table, diagram, or flowchart of the proposed OCS should be included. This representation may cross-reference other sections of Module 2.3 (e.g., 2.3.3 CQI).

KÖRBER

Local Control Strategies Do Not Ensure Final Product Quality





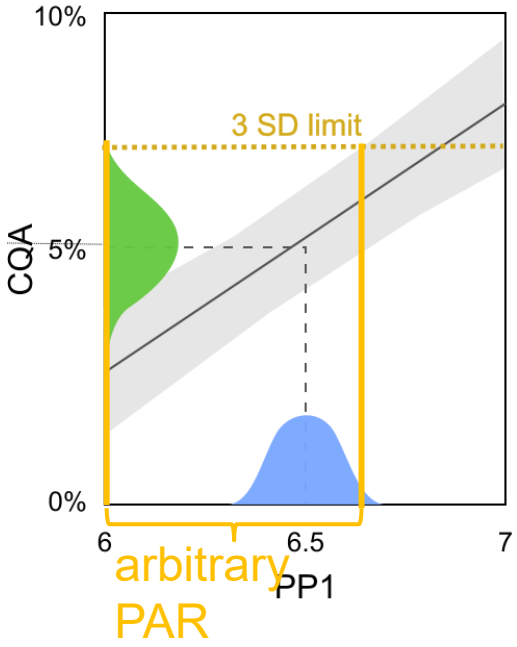


DS

Unit operation 1

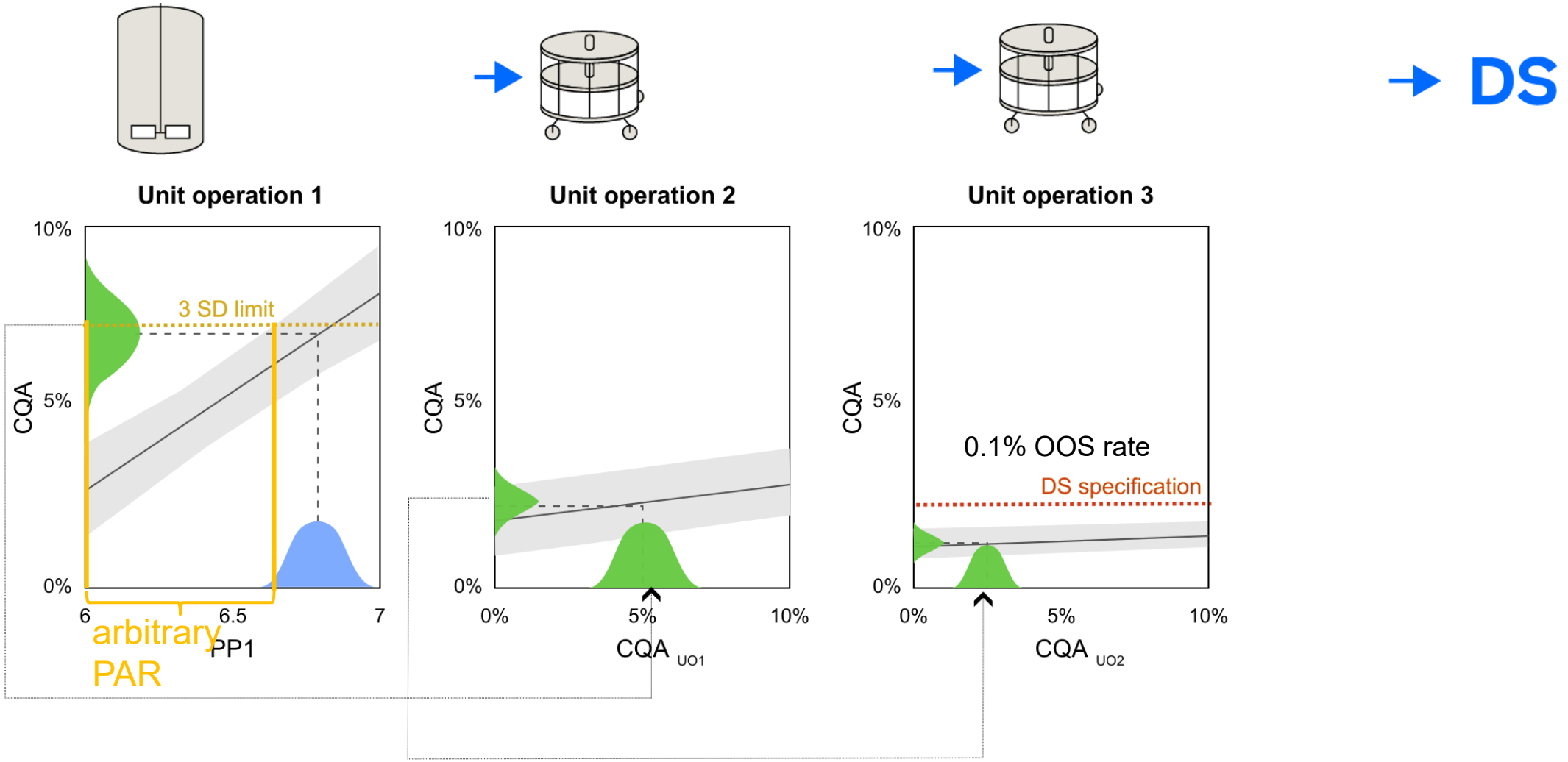
Unit operation 2

Unit operation 3

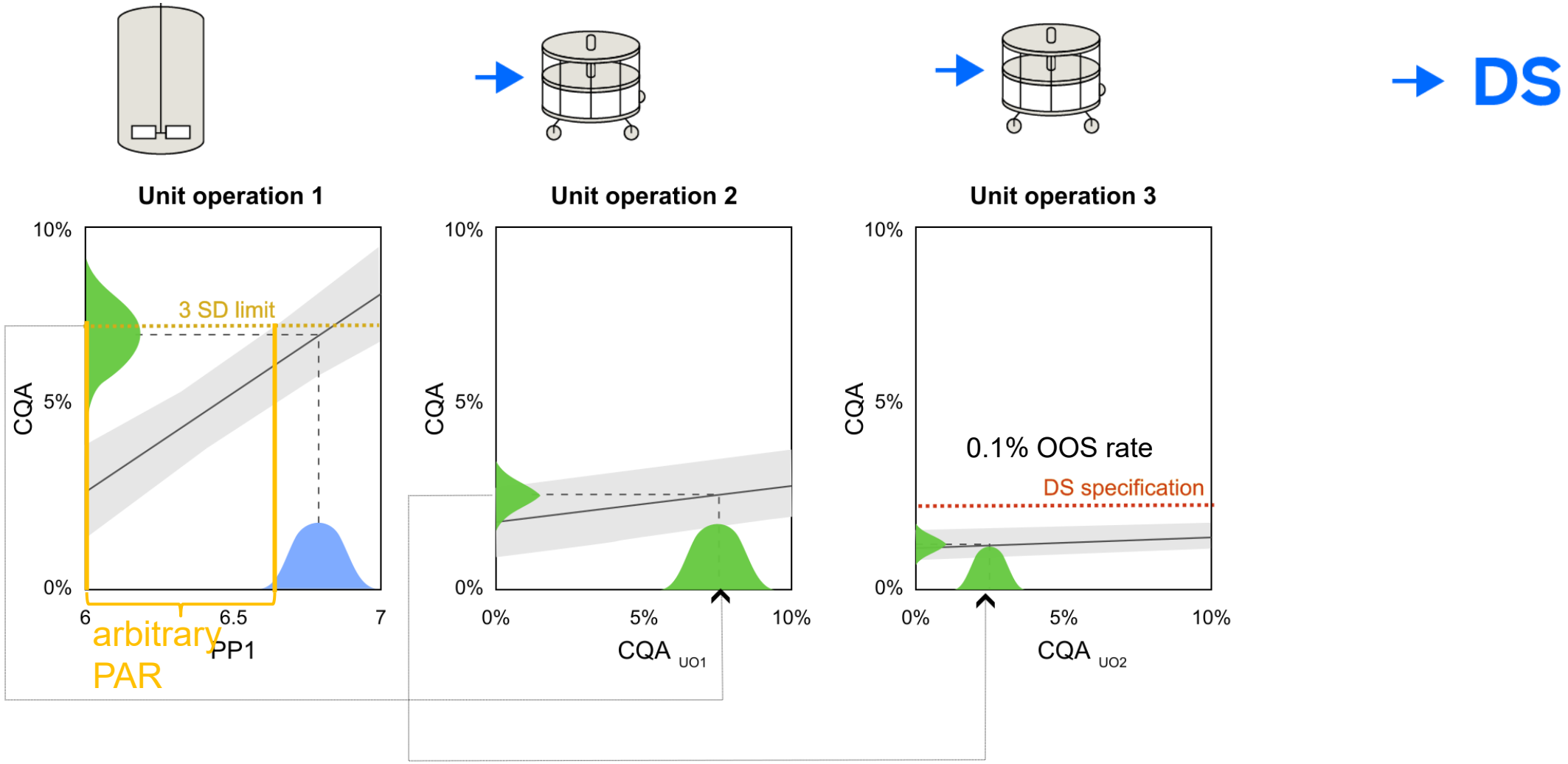


0.1% OOS rate

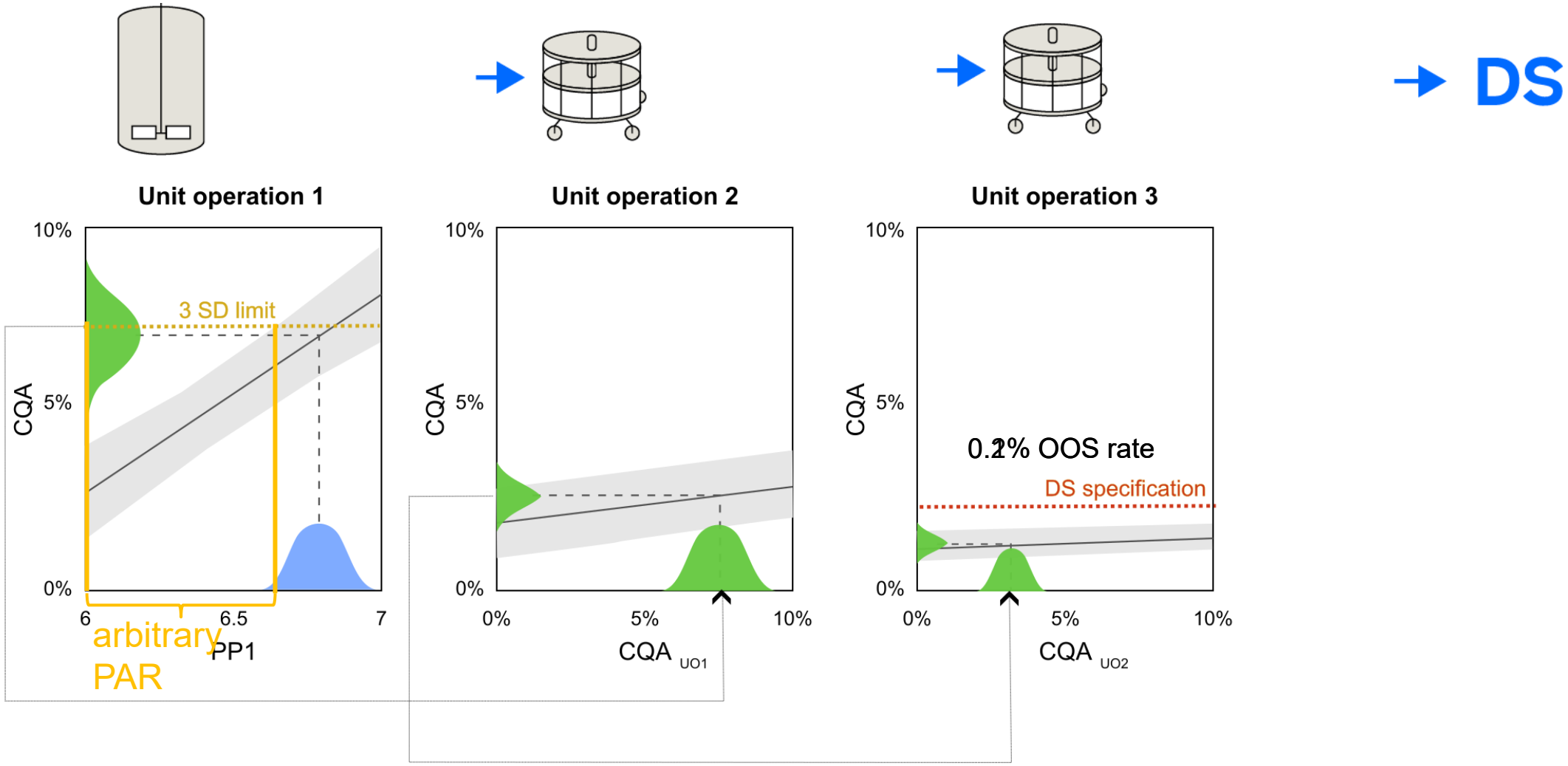
Local Control Strategies Do Not Ensure Final Product Quality



Local Control Strategies Do Not Ensure Final Product Quality

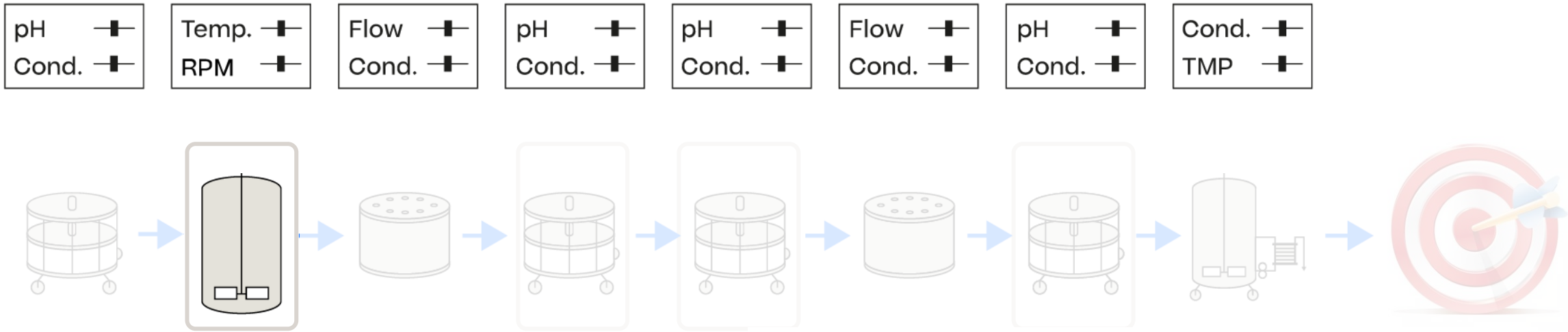


Local Control Strategies Do Not Ensure Final Product Quality

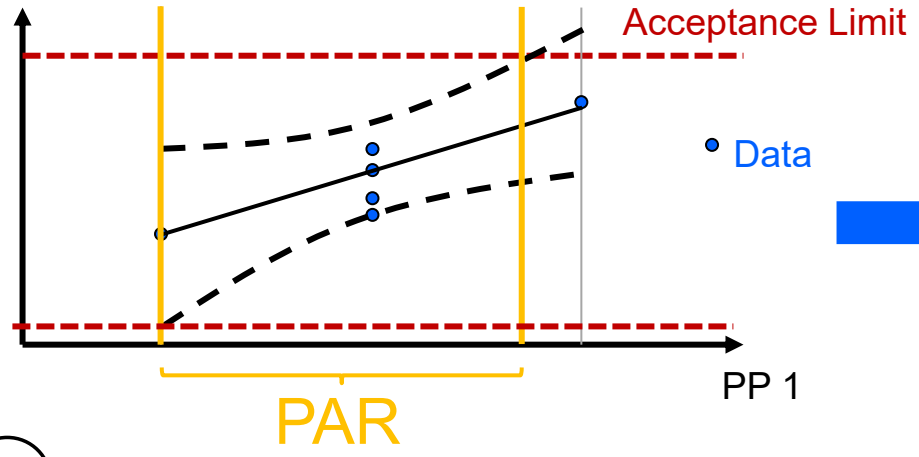


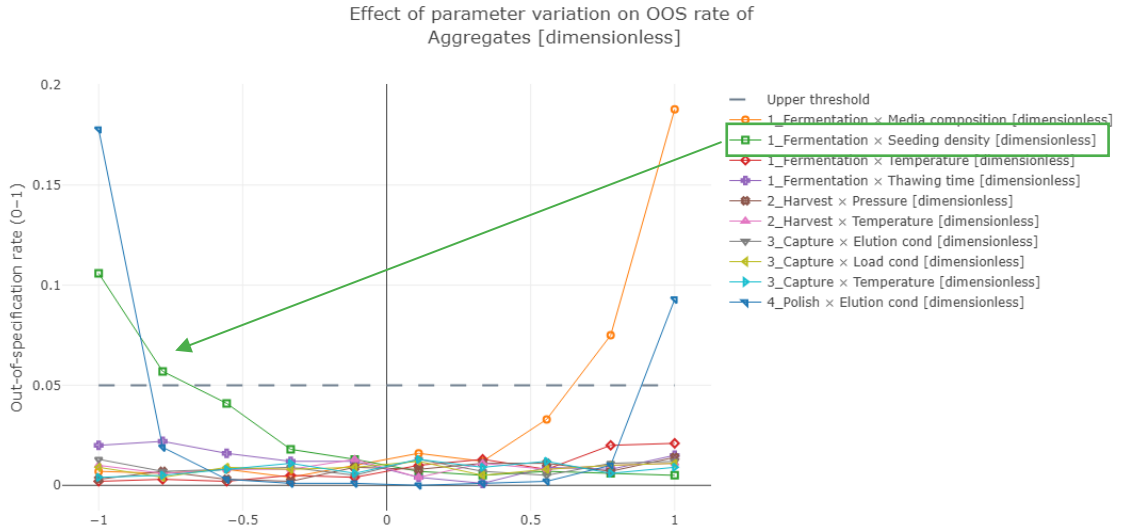
End-to-end process model identifies impact on final product quality

End-to-End Process Models as a Framework



CQA





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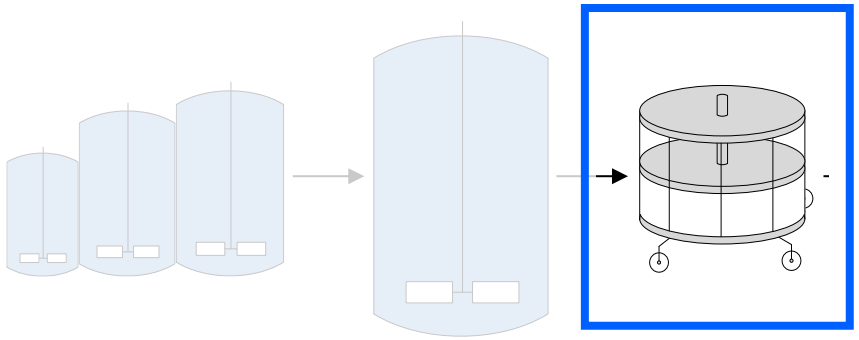
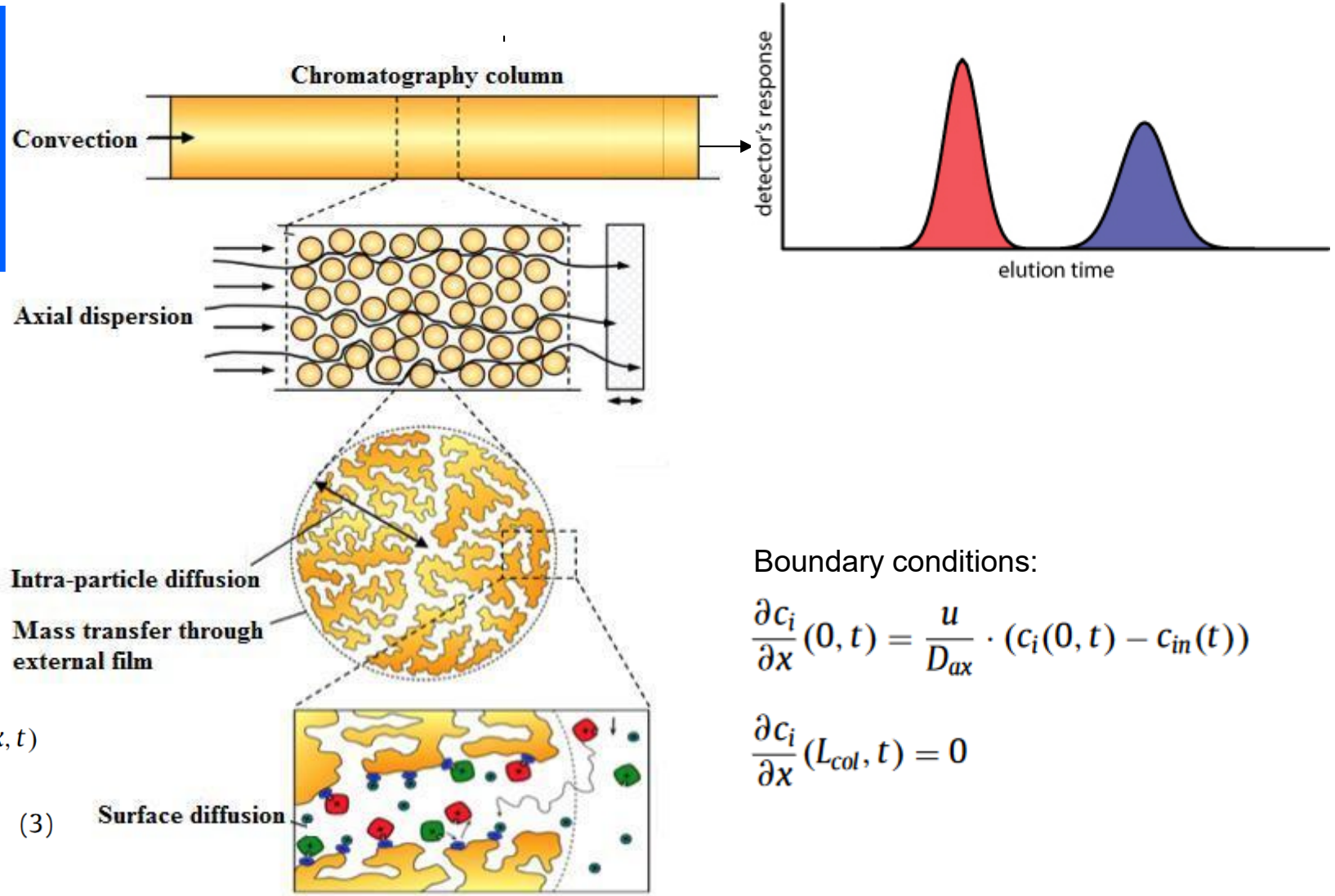
Only holistic control strategy allow to ensure quality of the product

Structure of Dynamic Models in DSP



$$\frac{\partial c_i(x,t)}{\partial t} = -\frac{u}{\varepsilon_{col}} \cdot \frac{\partial c_i(x,t)}{\partial x} + D_{ax} \cdot \frac{\partial^2 c_i(x,t)}{\partial x^2} - \frac{(1-\varepsilon_{col})}{\varepsilon_{col}} \cdot \left(\frac{3}{r_p} \cdot k_{eff}\left(c_i(x,t) - c_{p,i}(x,t)\right) \right)$$



$$\frac{\partial c_{p,i}(x,t)}{\partial t} = \frac{3}{r_p} \cdot \frac{k_{eff,i}}{\varepsilon_p} \cdot \left(c_i(x,t) - c_{p,i}(x,t)\right) - \frac{1-\varepsilon_p}{\varepsilon_p} \cdot \frac{dq_i(x,t)}{dt}$$

$$k_{kin,i} \cdot \frac{dq_i(x,t)}{dt} = k_{eq,i} \cdot \left(\Lambda - \sum_j \left(\nu_j + \sigma_j\right) \cdot q_j(x,t) \right)^{\nu_i} \cdot c_{p,i}(x,t) - q_i(x,t) \cdot c_s(x,t)^{\nu_i} \quad (3)$$

Boundary conditions:

$$\frac{\partial c_i}{\partial x}(0,t) = \frac{u}{D_{ax}} \cdot (c_i(0,t) - c_{in}(t))$$

$$\frac{\partial c_i}{\partial x}(L_{col},t) = 0$$

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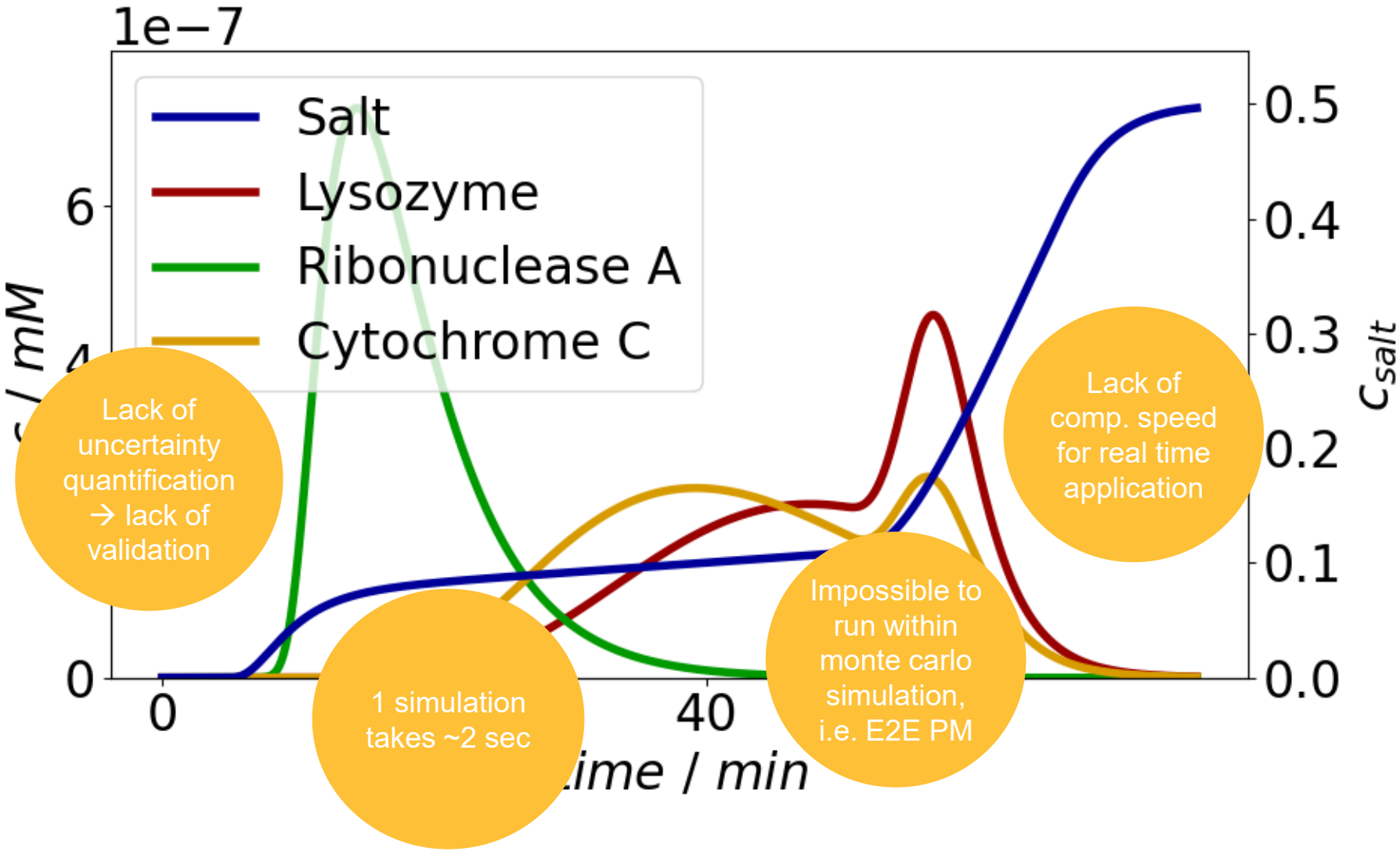
Known Bottlenecks of Conventional Mechanistic and Hybrid Models

Osberghaus et al. example on CEX column with SMA isotherm

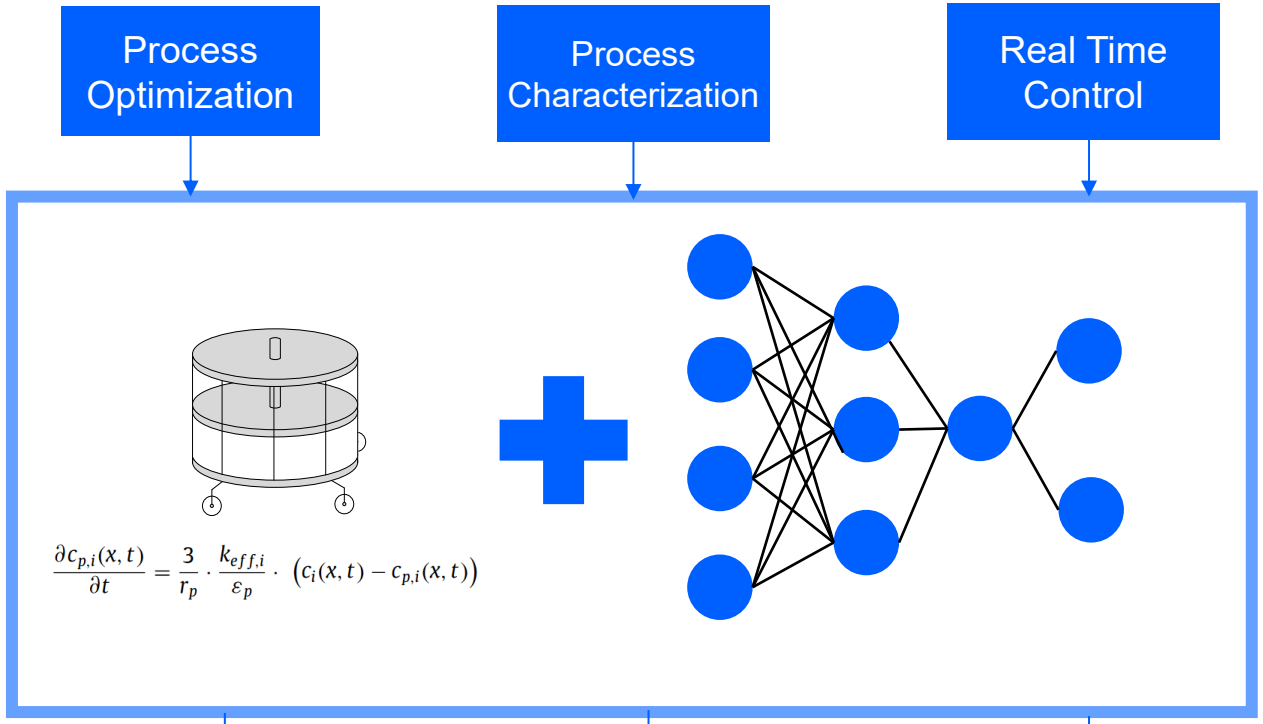


Physics Informed AI: A Disruptive Breakthrough Technology

Process Optimization

Process Characterization

Real Time Control



UNIQUE

- Immensely speed up computation time comp. to ODE/PDE solvers
- Ensure extrapolation by physical knowledge

Save runs due to physics knowledge

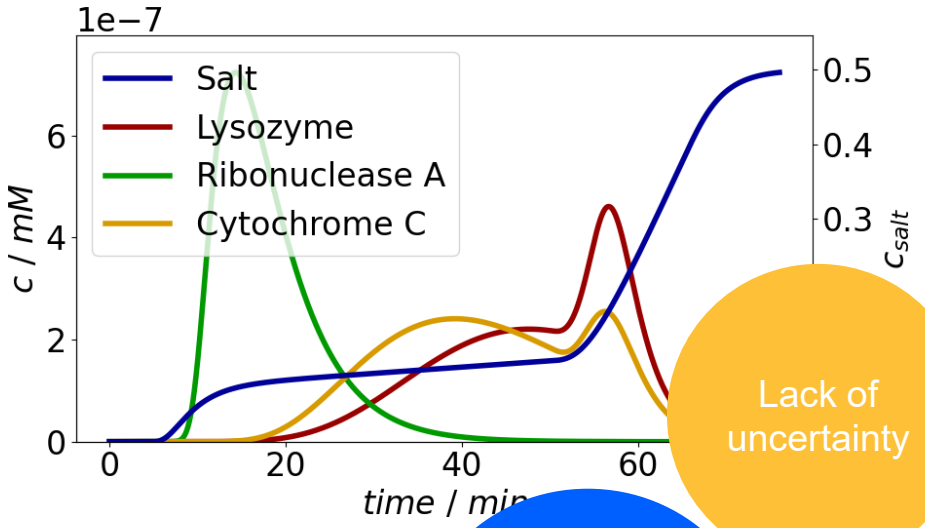
Enable model validation via uncertainty quantification

Enable real time control due to fast computation

Lower costs of good and increase sustainability

Proof of Concept: Speed Comparison of Conventional Solvers to Physics Informed AI

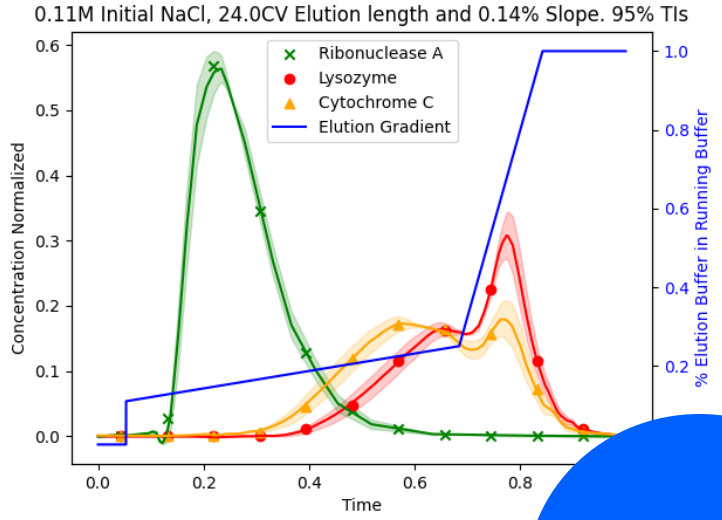
Gold Standard: CADET simulator



Lack of uncertainty

1 iteration: ~1.8 sec

Novel Physics Informed AI



1000 iterations: ~1.8 sec

1000 times faster on CPU!!!

Unvertainty intervals for dynamic models!

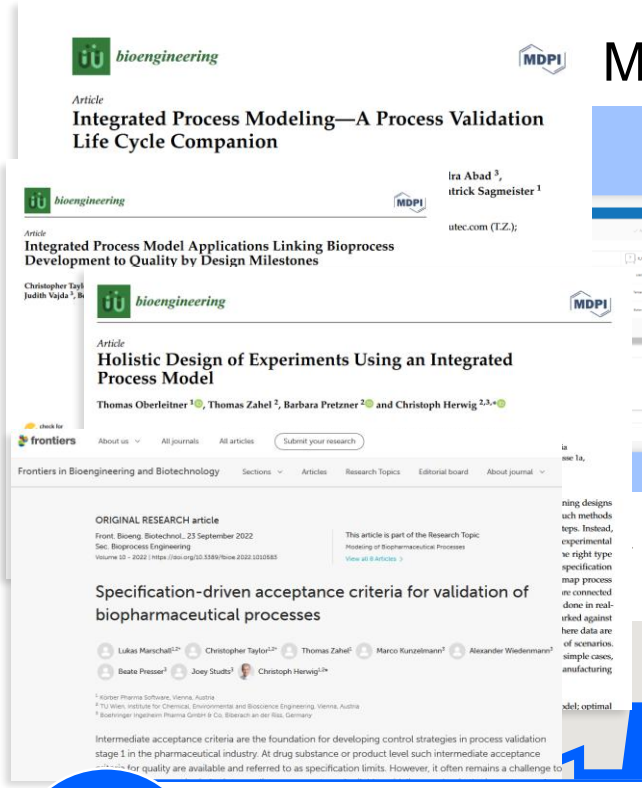
Capabilities of End-to-End Models, Digital Shadows and Digital Twins

Optimize process
Set Holistic Control Strategy
Speed-up process Development

Real-time prediction warnings/monitoring

Real-time optimization

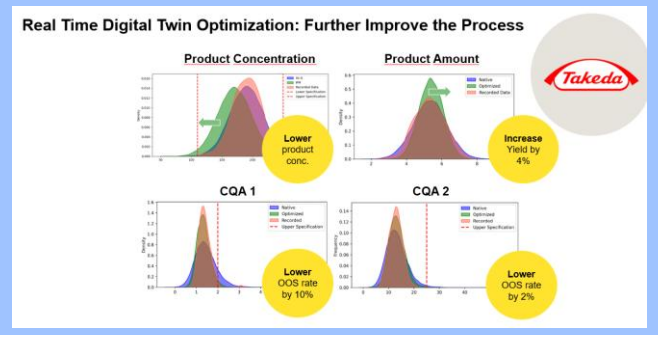
Model



Digital Shadow

https://virtual.ispe.org/p/s/end-to-end-digital-twins-as-life-cycle-companions-11293

Digital Twin



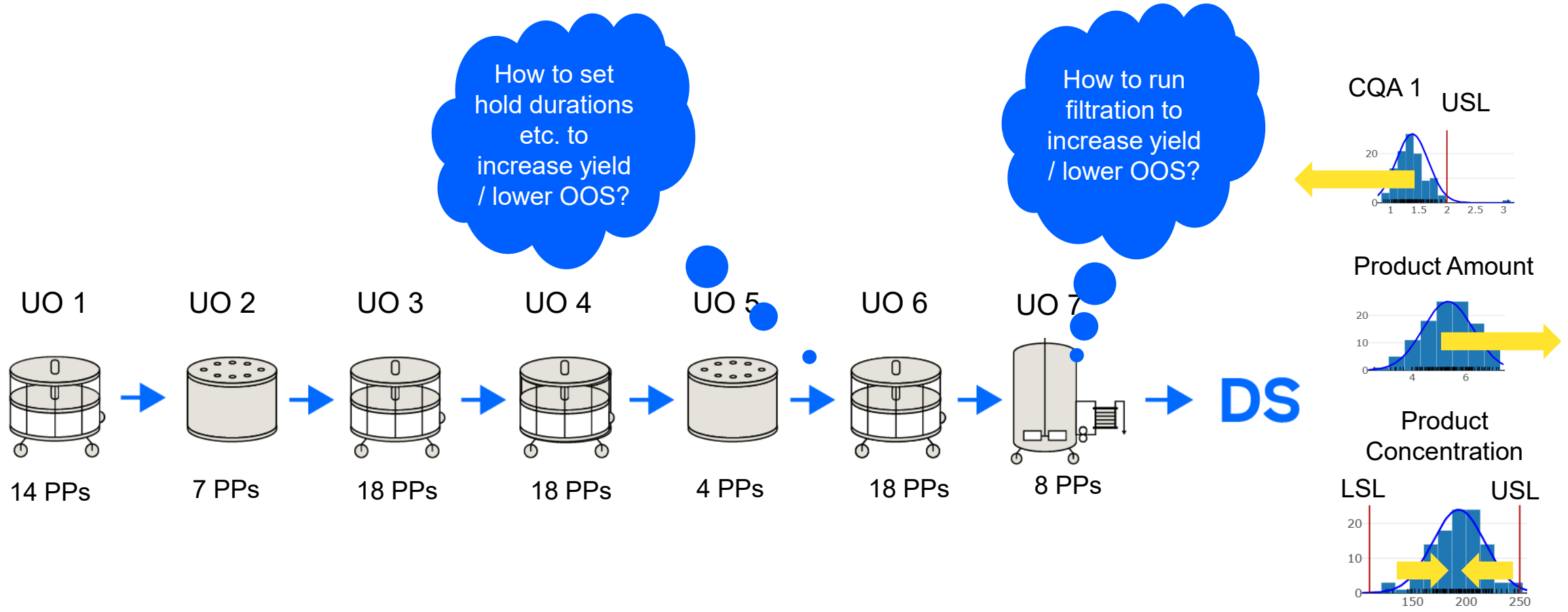
1 **Establish holistic control strategy and Save 70 % experiments in PD**

2 **Real-time monitoring and impact of deviations**

3 **Increase yield and quality by 5-10%**

Digital Twin @ Takeda

Takeda Question of Interest:
How to increase yield and meeting quality criteria at the same time?



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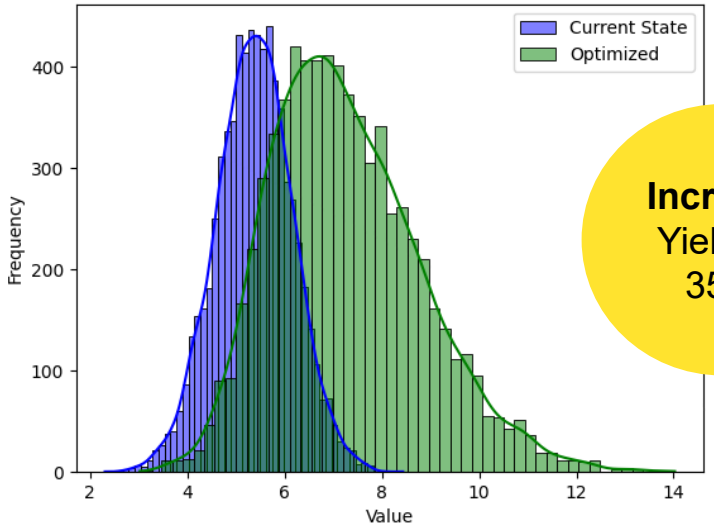
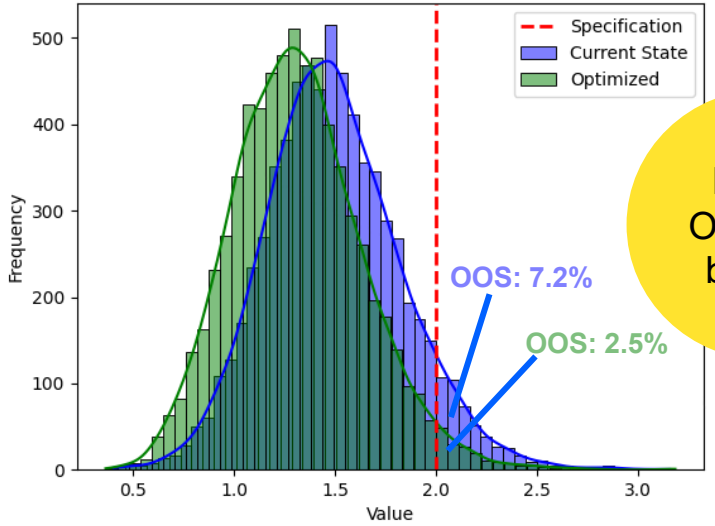
Process Model Offline Optimization Potential

Product Amount



Increase Yield by 35%

CQA 1



Lower OOS rate by 64%

Tunable PPs*	Hold Duration	TMP	Flow rate end	Flow rate start	Hold Duration	Process Duration
Unit Operation	UO 3	UO 4	UO 4	UO 4	UO 7	UO 6
Current State	5.7	0.5	318.9	345.6	8.1	23.4
Optimized	**9.0**	**0.7**	**215.6**	**411.7**	**3.1**	**20.6**

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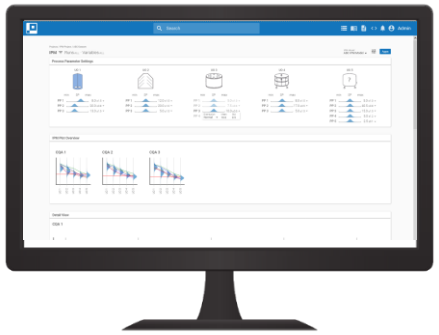
Takeda Use Case Description of the Digital Twin

Measurable process parameters are sent to the process model via established interfaces (mature and used also for other tools)



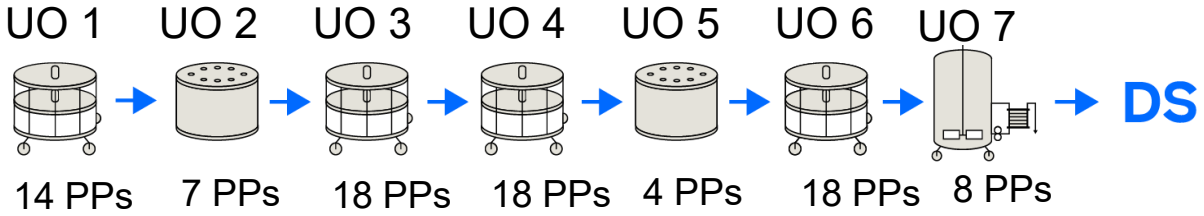
End-to-end process model predicting final CQA & product amount as a function of PP of all steps

Recommendations how to change the setpoint of **tunable process parameters** are sent to the MES system for human approval

MES

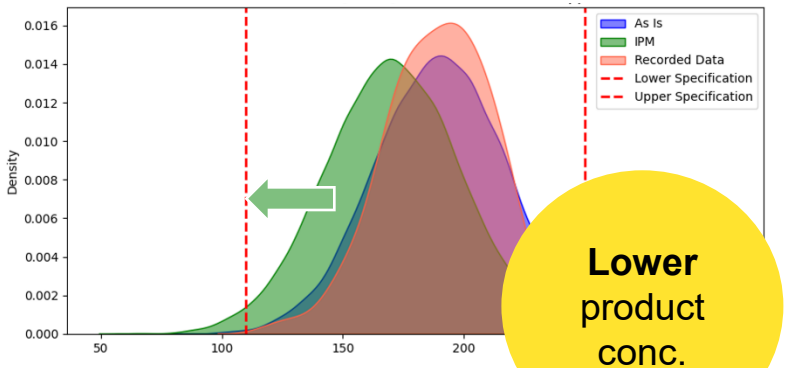
Middleware

Other IT system



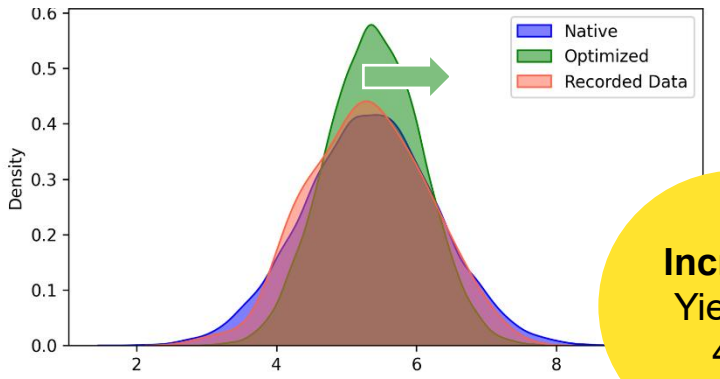
Real Time Digital Twin Optimization: Further Improve the Process

Product Concentration



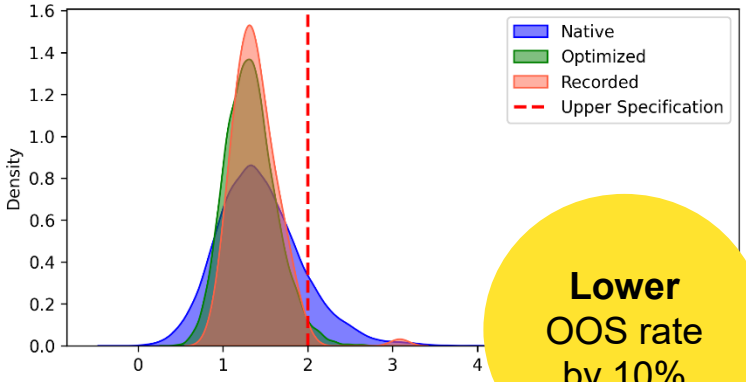
Lower product conc.

Product Amount



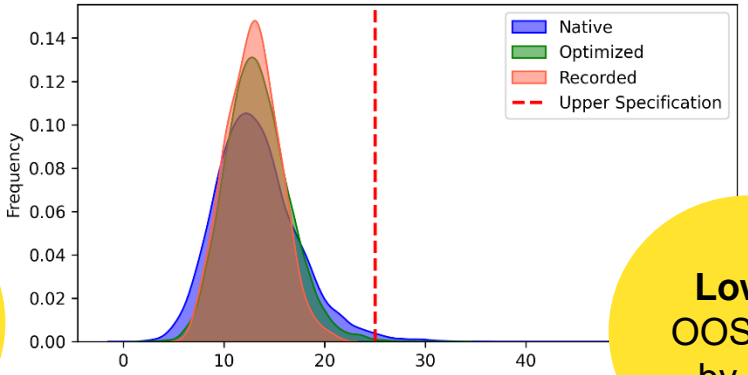
Increase Yield by 4%

CQA 1



Lower OOS rate by 10%

CQA 2



Lower OOS rate by 2%

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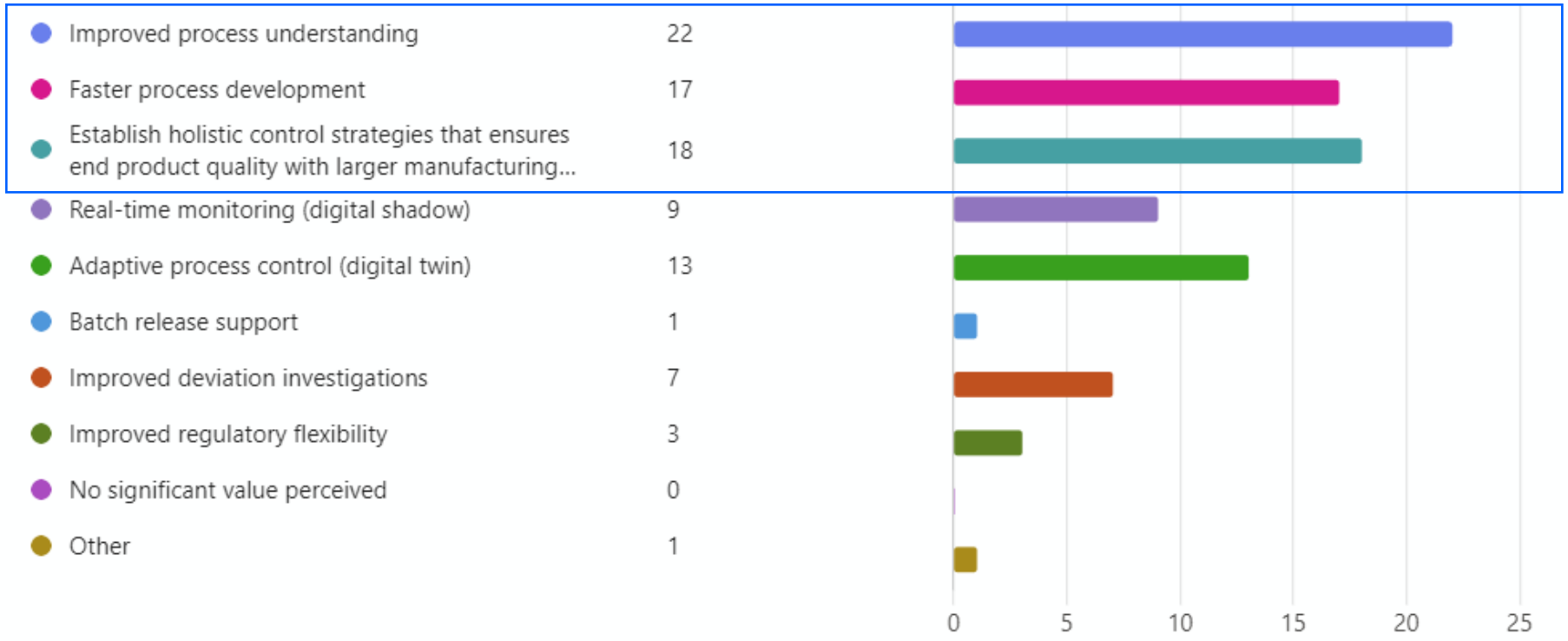
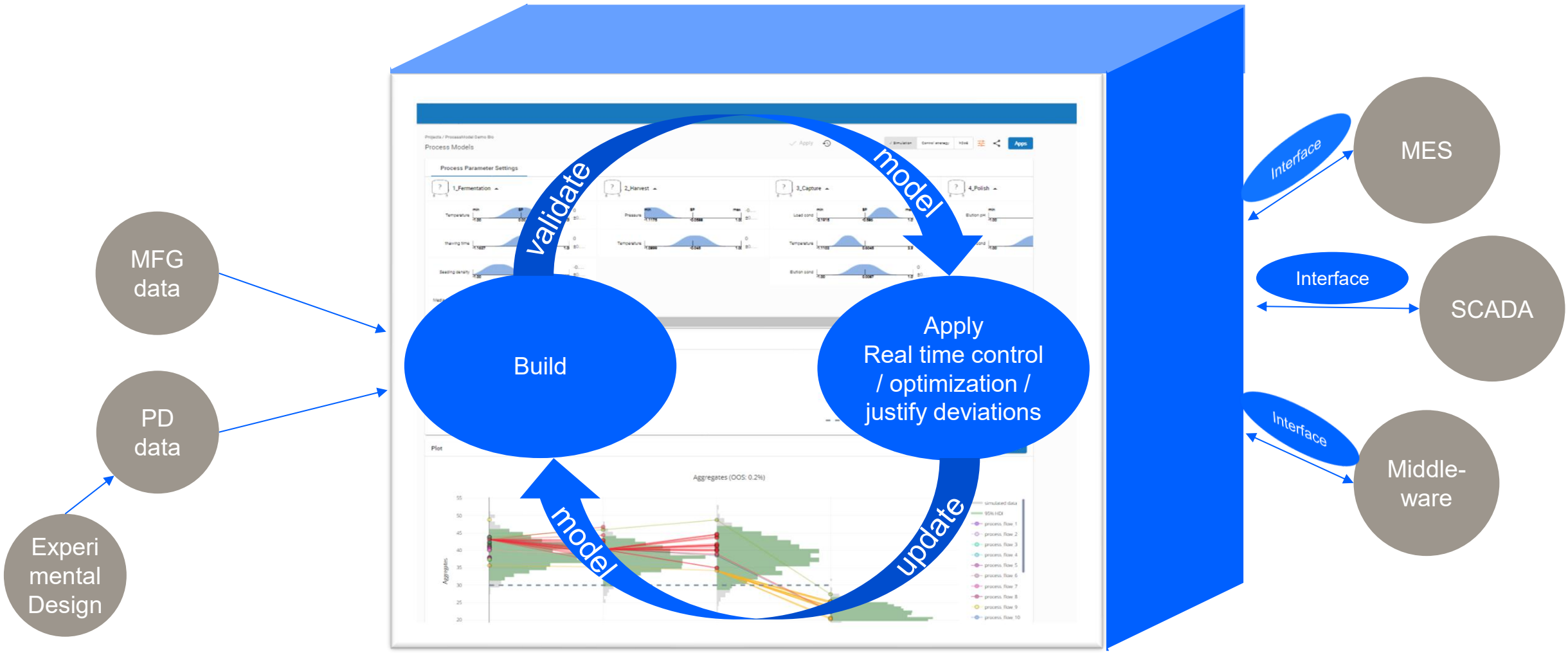
Survey: Perceptions and Barriers Regarding Advanced Modelling and Adaptive Control Strategies – 34 participants

4. In which areas do you believe advanced integrated/end-to-end process models could provide the greatest value?

More details



Model Lifecycle & Validation



Verification, Validation and Uncertainty Quantification

ASME V&V 40 risk-informed credibility assessment framework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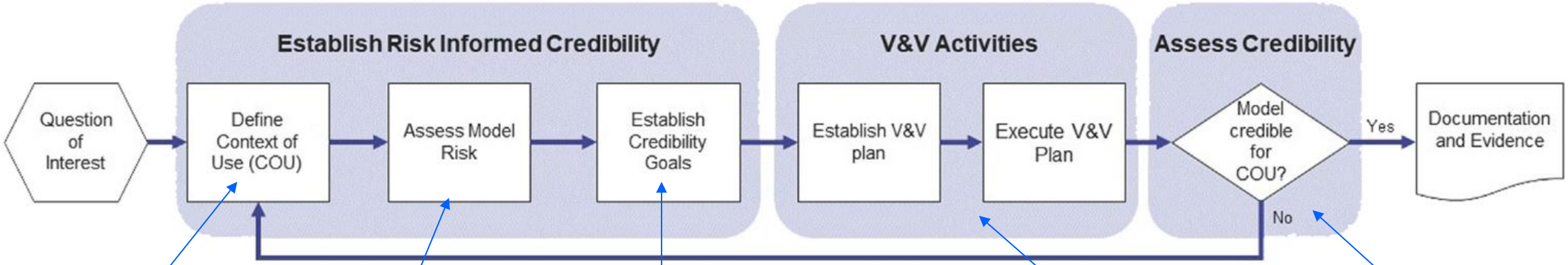
Rapid Communication

Verification and Validation of Computational Models Used in Biopharmaceutical Manufacturing: Potential Application of the ASME Verification and Validation 40 Standard and FDA Proposed AI/ML Model Life Cycle Management Framework

Gautier Bideault [a, f], Anthony Scaccia [b, f], Thomas Zahel [c, f], Robert W. Landertinger [d], Chathuri Daluwatte [e, *]

[a] Sanofi Pasteur, Val de Reuil, France
[b] Sanofi Pasteur, Swiftwater, PA, USA
[c] Werum IT Solutions GmbH, Vienna, Austria
[d] Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany
[e] Sanofi, Cambridge, MA, USA



Which model?
How will the model be used?

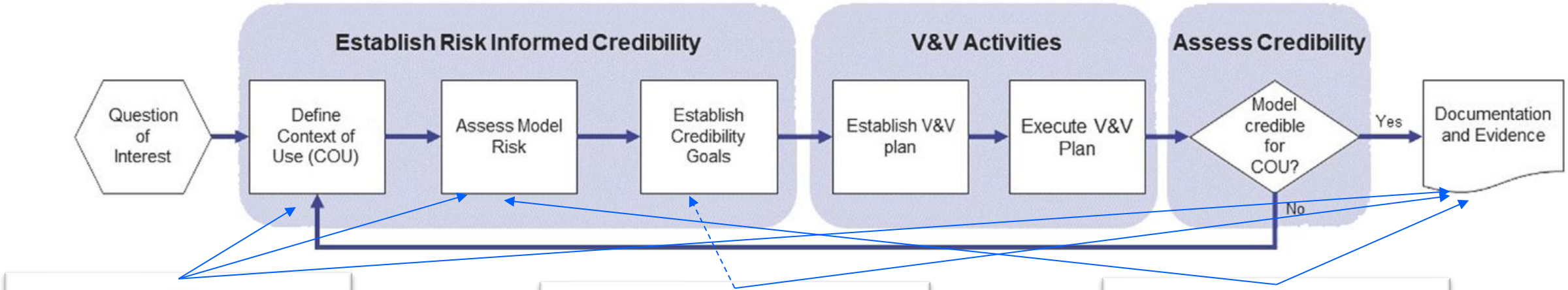
What is the risk to product quality?

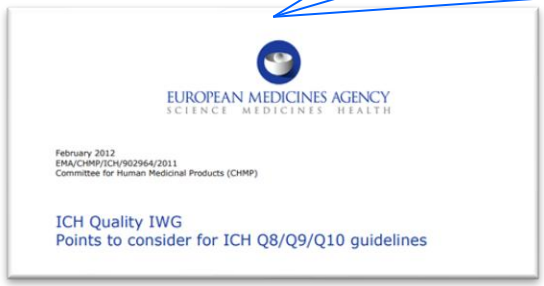
- Accuracy
- Generalizability
- Numerical stability
- Assumptions: General model assumptions based on model type
- ….

- E.g. RMSE, Leverage of individual runs, R^2-Q^2, externally studentized residuals

Applicability: Check if the model works as required for the context of use

Regulatory Landscape Dealing with Process Model Validation





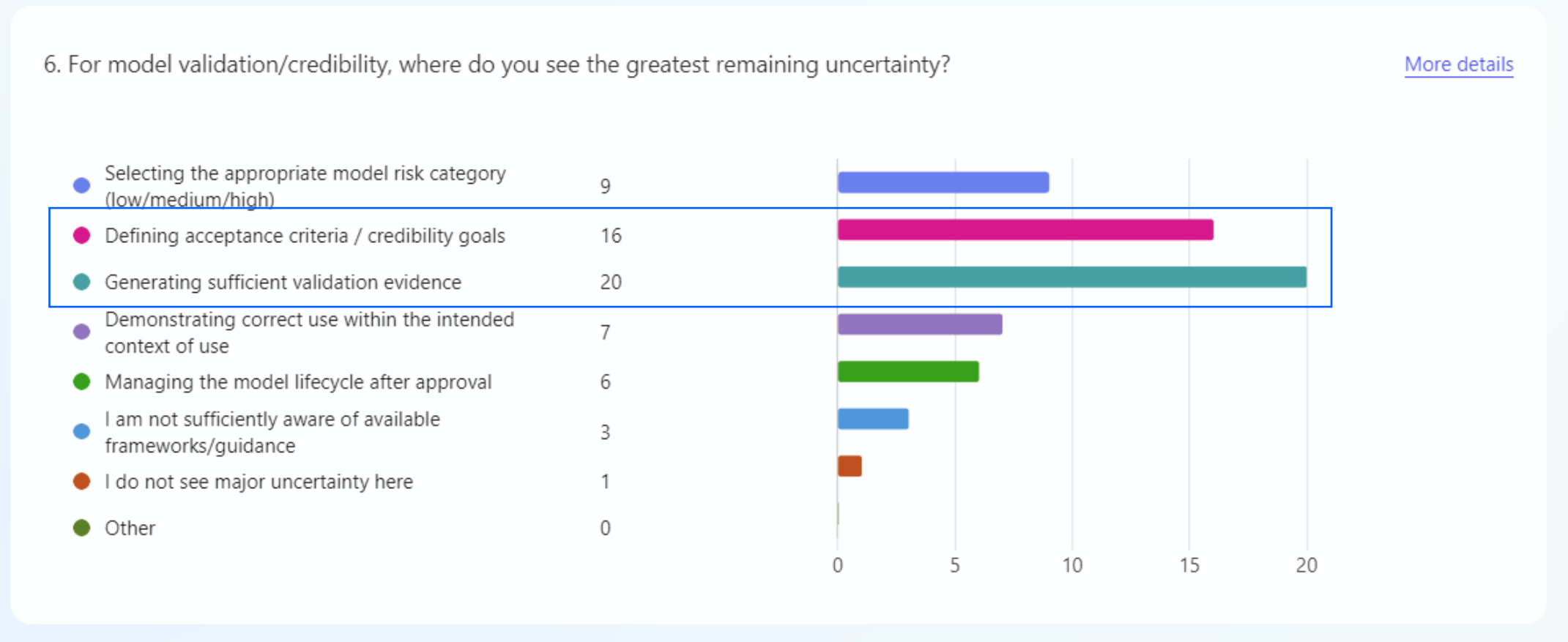
- Focus of on “5. Role of Models in QbD”
- Categorization of models (low/medium/high) commensurate with model’s contribution in assuring the quality of the product
- Development workflow for models
- What to be reported in submissions

- Credibility goals for DOE type of models mentioned (ANOVA; p-values,
- Submission of design space models

- Categorization of model risk (low/medium/high)
- What to report in a dossier

Current EMA/FDA guidance defines elements and expectations of model validation, but does not define a structured, end-to-end validation workflow comparable to V&V frameworks

Survey: Perceptions and Barriers Regarding Advanced Modelling and Adaptive Control Strategies – 34 participants



ICH Q2(R2) is explicit on Validation Workflow and Performance Characteristics

- ICH Q2 describes a clear validation workflow and states performance characteristics to be demonstrated
  - Accuracy
  - Precision
  - Specificity
  - Repeatability
  - …
- A true workflow and acceptance criteria / credibility goals per model type are missing for process models

Figure 1: Validation study design and evaluation

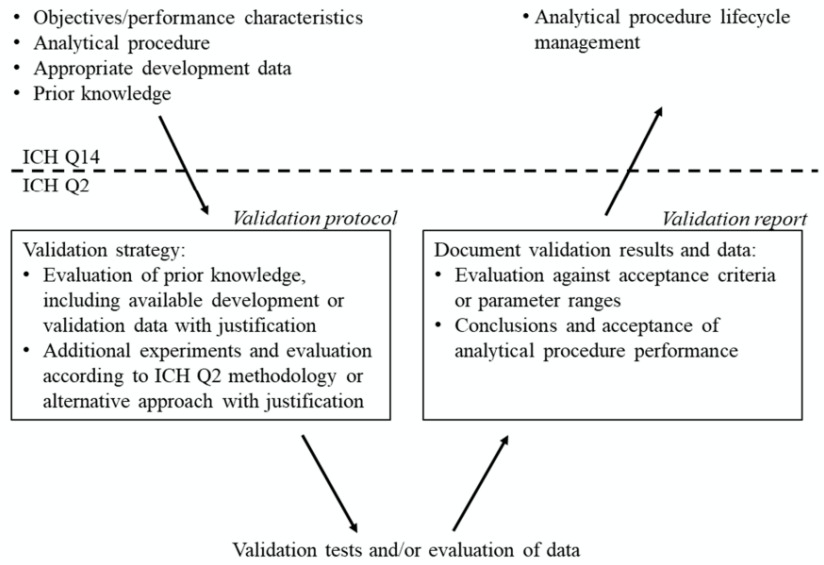


Table 1: Typical performance characteristics and related validation tests for measured quality attributes

Measured Quality Attribute / Analytical Procedure Performance Characteristics to be Demonstrated (2)	Identity	Impurity (Purity)		Assay
		Other quantitative measurements (1)		Content or potency
		Quantitative Test	Limit Test	Other quantitative measurements (1)
Specificity (3)				
Specificity Test	+	+	+	+
Range				
Response (*Calibration Model*)	-	+	-	+
Lower Range Limit	-	QL†	DL	-
Accuracy (4)				
Accuracy Test	-	+	-	+
Precision (4)				
Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

Credibility Goals for Process Models

Verification & Validation activates are specific to (1) context of use and (2) model type. General considerations should include:

- ❑ Check **choice model** form
- ❑ Check if **input data** for modelling is **representative for final process**
- ❑ **Check model assumptions**
- ❑ Check **uniqueness of model (numerical stability)**
- ❑ Check model accuracy vs. required accuracy
- ❑ Check for **generalization** on (challenging) **unseen test data**

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Rapid Communication

Verification and Validation of Computational Models Used in Biopharmaceutical Manufacturing: Potential Application of the ASME Verification and Validation 40 Standard and FDA Proposed AI/ML Model Life Cycle Management Framework

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ABSTRACT

A wide variety of computational models covering statistical, mechanistic, and machine learning (locked and adaptive) methods are explored for use in biopharmaceutical manufacturing. Limited discussion exists on how to establish the credibility of a computational model for application in biopharmaceutical manufacturing. In this work, we tried to use the American Society of Mechanical Engineers (ASME) Verification and Validation 40 (V&V 40) standard and FDA proposed AI/ML model life cycle management framework for Software as a Medical Device (SaMD) in biopharmaceutical manufacturing use cases, by applying to a set of curated hypothetical examples. We discussed the need for standardized frameworks to facilitate consistent decision making to enable efficient adoption of computational models in biopharmaceutical manufacturing and alignment of existing good practices with existing frameworks. In the study of our examples, we anticipate existing frameworks like V&V 40 can be adopted.
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Table 2
Credibility Activities and Associated Credibility Goals as Defined in V&V 40 Standard.

Activities	Credibility Factors		Credibility Goals
Verification	Code	Software Quality Assessment (SQA)	The level of SQA is informed by model risk. The rigor of SQA can be anywhere between no SQA to rigorous anomaly lists based on model risk.
		Numerical code verification	Captures how well the code solves compared to a known benchmark. The rigor for numerical code verification can be anywhere between not performed to rigorous numerical code verification.
	Calculation	Discretization error *The term Discretization error is not frequently used with models used in biopharmaceutical manufacturing. Similar concept may be sampling interval for time series and/or sampling strategy to acquire required granularity in data.	Captures the error associated with chosen mesh for finite element models. Similar concept for statistical and ML models may be granularity of the validation dataset. E.g. If an input has the range of 1 −10 for the COU, whether to cover the range with increments of 1 or increments of 0.1 during verification is informed by the model risk. The rigor for verification can be anywhere between not performed to rigorous verification.
		Numerical solver error	Test whether same output is reproduced in the computational environment. The rigor for verification can be anywhere between not tested to rigorous testing.
		Use error	Test the human error e.g.: outputs when typed a wrong value. The rigor for verification can be anywhere between no User Acceptance Testing (UAT) to rigorous UAT.
Validation	Computational model	Model Form	Confirm that the model form is suitable for the QOI and COU.
		Model inputs	Confirm that the model inputs are suitable for the QOI and COU.
	Comparator	Test samples	Confirm that the test samples sufficiently cover QOI and COU (e.g.: sample size, sampling rate/granularity).
		Test conditions	Confirm that the test conditions sufficiently cover QOI and COU (e.g. conditions samples were collected).
	Assessment	Equivalency of input parameters	Assess the similarity/difference between the model input data to that of the real-world scenarios the model will operate in (e.g.: experiment conditions, stratification of test dataset). This informs the credibility of the model for the COU and QOI (e.g. whether the inputs used in V&V activities covered all scenarios the model will operate in real-world).
		Output comparison	Assessing the equivalency of outputs from model with respect to the experiment or test dataset is done using *performance metric and acceptance criteria* combinations. As an example, assume one of the selected performance metrics for a regression model is R^2. Then, an example of the model risk informed acceptance criteria for R^2, would be, strictly set criteria for a high-risk model i.e. $R^2 > 0.99999$ while for a low risk model, the acceptance criteria would be less strict i.e. $R^2 > 0.8$.
Applicability		Relevance of the validation activities to QOI Relevance of validation activities to the COU	Determination that the V&V plan sufficiently cover the model operating domain in terms of COU and QOI.

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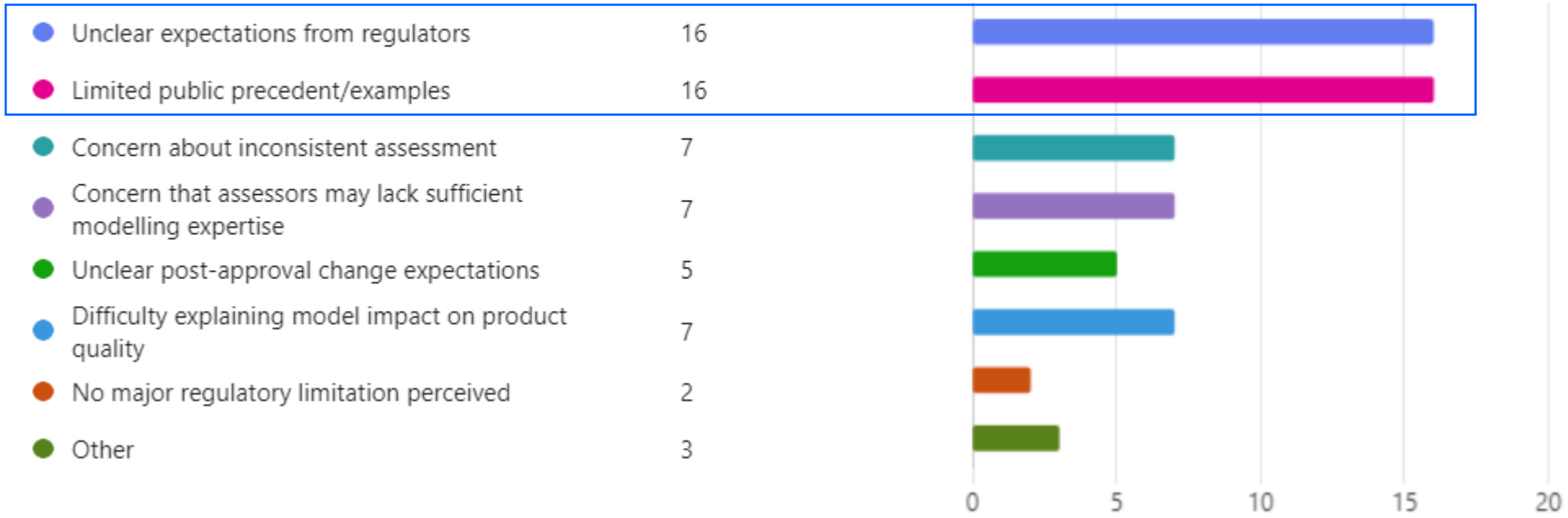
Model types are limited (data driven, mechanistic, hybrid) and general and specific credibility goals would be possible to harmonize/agree on

7. What regulatory factors most limit use of advanced models in filings or GMP implementation?

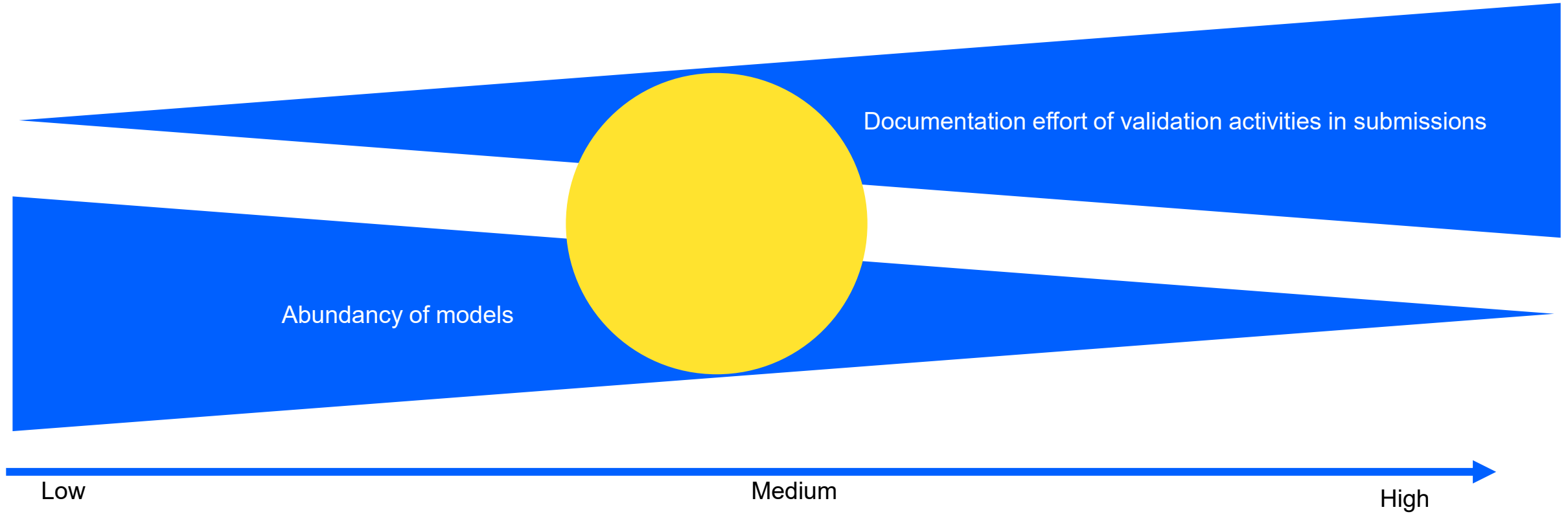
More details



Maybe the fear of being the “first mover”?

How Can We Generate Experience i.r.t Model Validation?

Medium risk models would be a good place to gain experience and have a common learning curve on model validation
Clear definition on what is medium risk is required!



Conclusions

- End-to-end process models enable to model what really matters → final product quality. It has been shown and published that those model should be applied as:
  - Offline process models: holistic control strategy ensuring meeting final product quality (low OOS)
  - Digital Shadows (monitoring of manufacturing)
  - Digital Twins (manufacturing Control) with increased yield and quality
- Physics informed AI models can help to speed up solution and application of mechanistic models in End-to-End Process Models (within Monte Carlo Simulation)
- Regulatory expectations may be clarified to reduce uncertainty and increase efficiency during model validation:
  - Workflow that includes general principles of credibility/acceptance criteria and validation protocol and execution (similar to ICH Q2 / Q14 for analytical method development)
  - Clear definition and looking into medium critical models to gain experience for all stakeholders, even if this is supporting information

Thank you!

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