Machine Learning-Supported (Process) Models:

Promises and Practical Implementation Challenges

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Introduction: Promises and Challenges

Promises and Challenges of AI in Manufacturing

Opportunities of AI in Manufacturing

- Enhancing process control,
- Increasing quality,
- Speeding up drug development,
- Optimizing process design (e.g., Digital Twins),
- Efficient and integrated monitoring/maintenance programs.

Challenges of AI in Manufacturing

- Lack of harmonized standards for AI validation (bridging IT/GMP terminology).
- Ambiguity in validation and lifecycle management requirements.
- Uncertainty and inconsistency on regulatory expectations from Health Authorities.
- Evolving regulatory guidance and the need for alignment between regulators and manufacturers.
- Broad regulatory and compliance spectrum for AI/ML application (Non-GMP, GMP, and GMP & Registration, e.g., Digital Twin evolution) ? dossier or PQS only?
- Potentially slow post-approval implementation due to high requirements and long global registration timelines.

→ balance between ensuring safe and robust use and encouraging innovation to accelerate medicine accessibility

Assessment Framework

Model Assessment Principles Using a Two-Dimensional Matrix

- **Risk-Based Credibility Assessment:**
  Regulatory oversight must be commensurate with the risk the model poses to product quality

- **The Two-Dimensional Matrix:** evaluates model's credibility by balancing its level of influence against the severity of decision consequences:
  - Decision Consequence: The significance of an adverse outcome that could result from an incorrect model-based decision concerning the question of interest
  - Model Influence: Context of Use, the weight of the model's contribution relative to other evidence in the totality of the decision

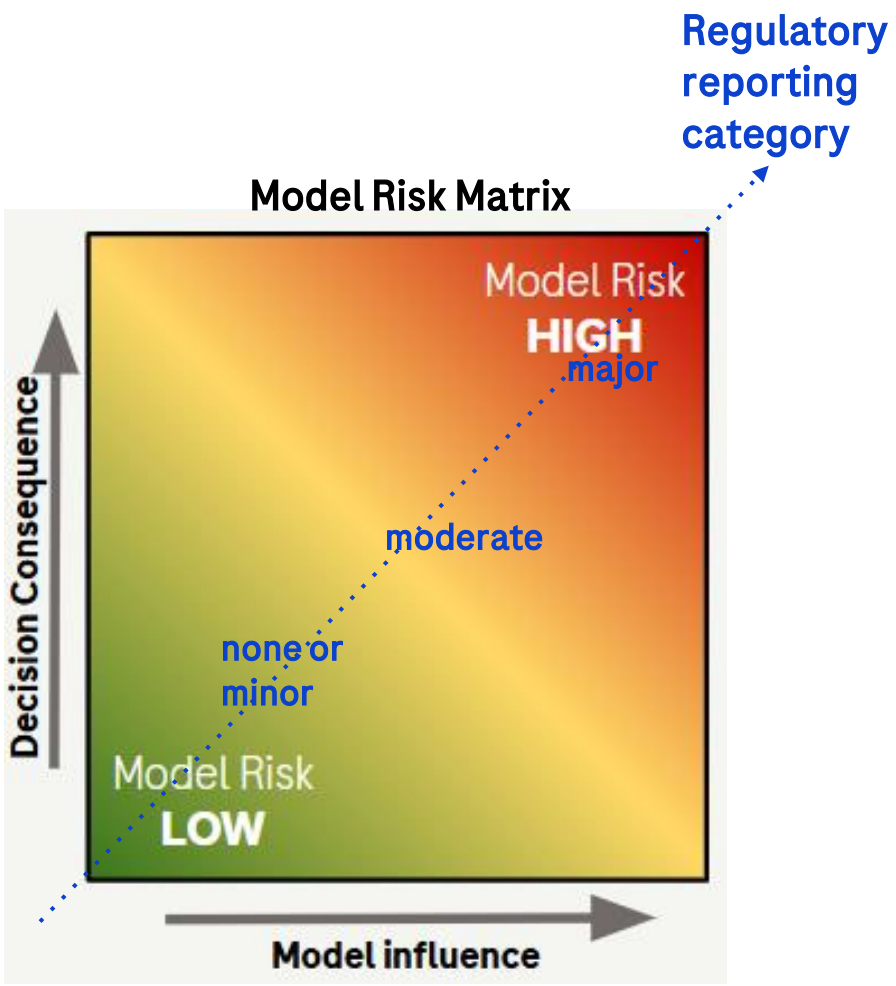
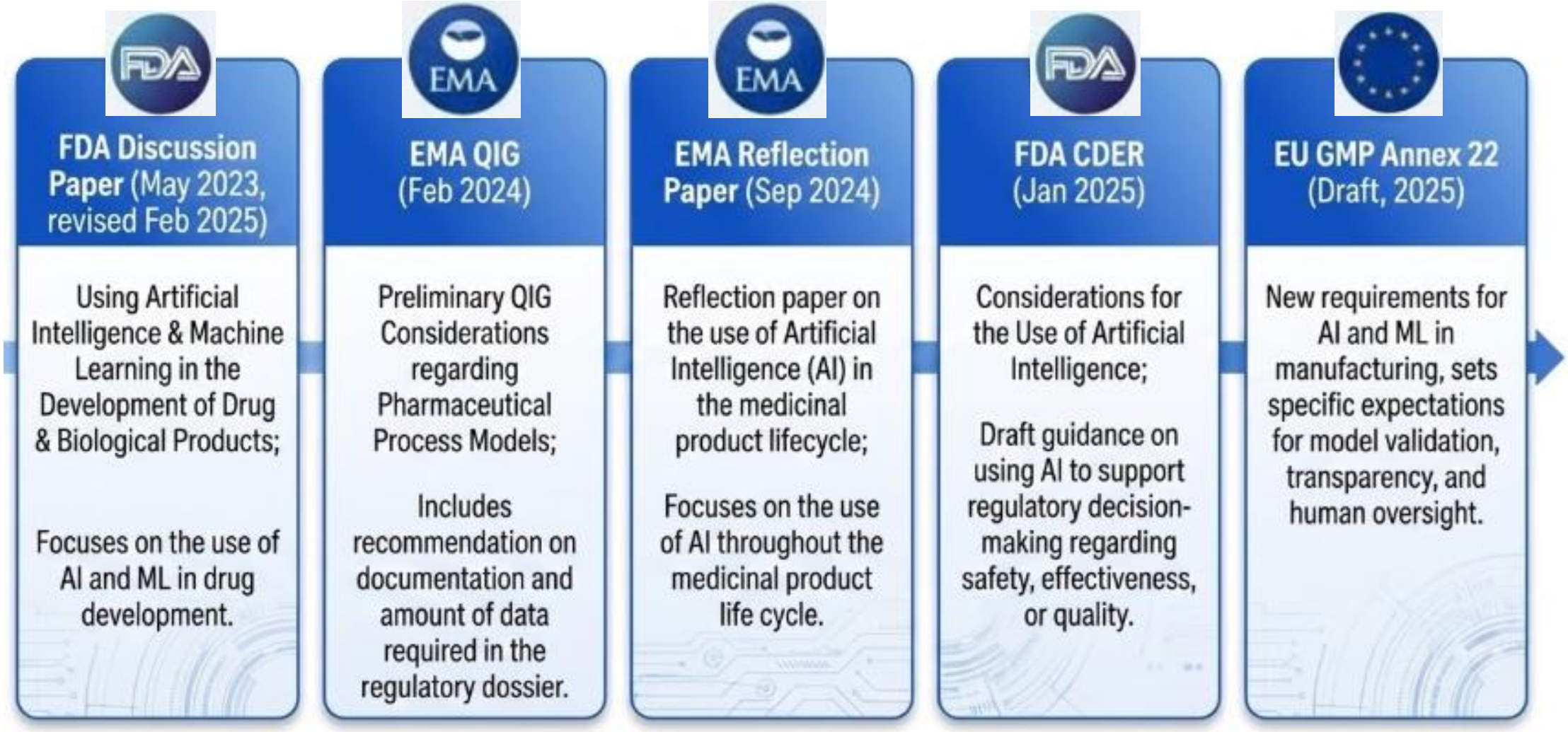


Image source (adapted): Assessing the credibility of computational modeling through verification and validation: Application to medical devices V&V 40, 2018c

Emerging Regulatory Guidance Landscape



Case Study 1 – Model for Predicting Critical Quality Attribute in mAB

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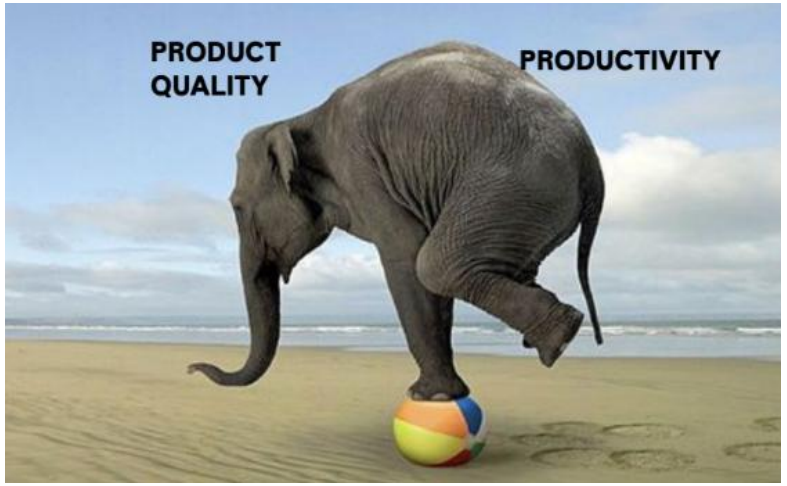
Model Overview



- The WHY: Balancing Productivity and Product Quality Risk
- The WIN: Cell culture process optimization (real-time in-batch),

  to ensure high product yield (titer)

  AND

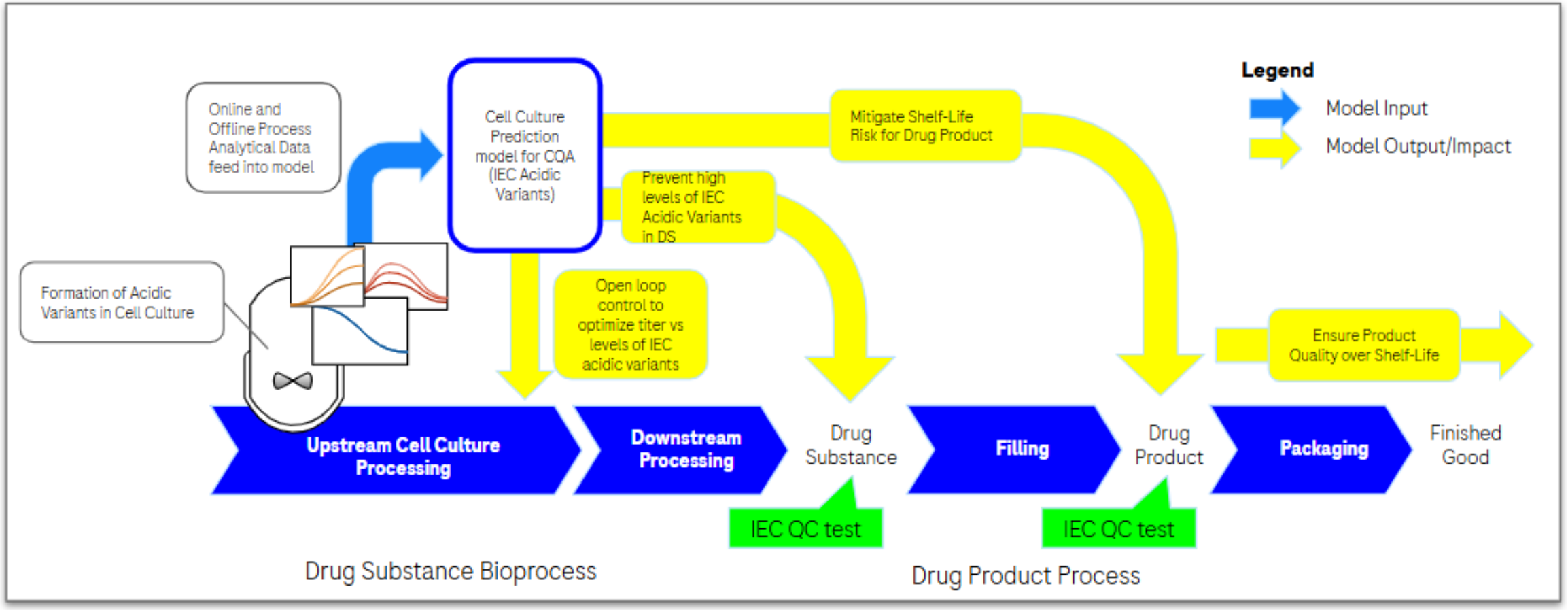
  CQA IEC Acidic Variants meets robustly DS and DP release and

  shelf-life limits.
- Operational Mode: open loop (qualified human intervention)
- Machine Learning: was used for development of model;

  model itself is a deterministic regression model that uses a fixed formula for calculation/prediction
- Implementation Status:
  - concept and development phase, no manufacture has taken place
  - planned to be implemented post-approval to an already registered commercial product

Case Study 1 – Visualization Predictive Critical Quality Attribute Model

Visualization of Predictive CQA Model for Open-loop Control



Open loop control = human SME decision, based on model output and other process controls (e.g. registered harvest time window).

Case Study 1 – Context of Process Model in the Control System

The goal of a future model deployment is to allow in-batch optimization of cell culture titer while preventing high levels of the CQA IEC acidic variants.

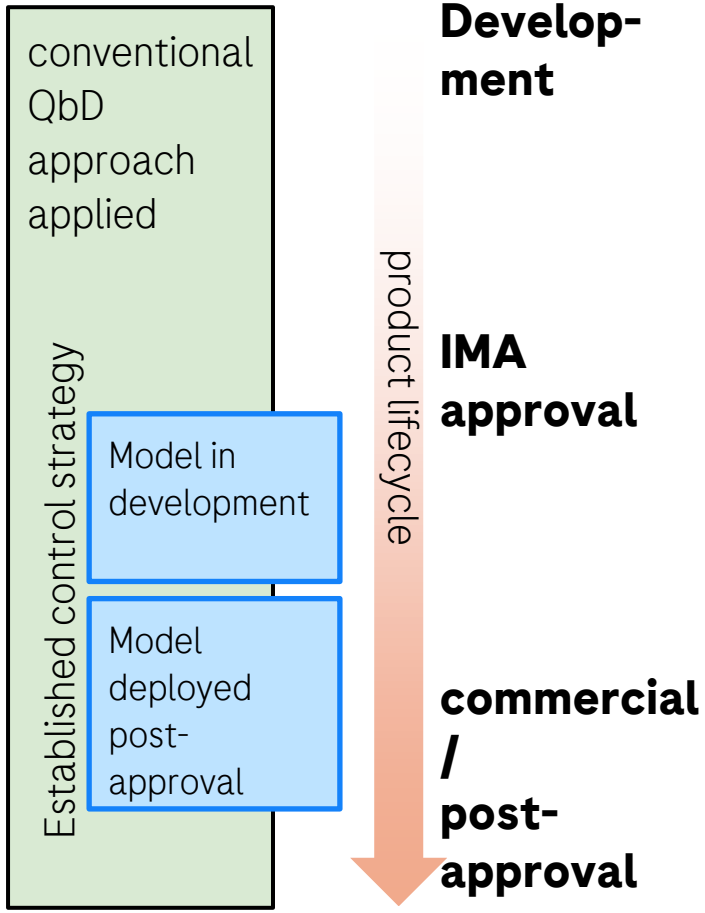
The initially developed process and validated acceptable ranges of the registered control strategy will be retained during lifecycle for manufacturability:

- QC analytical procedure and specifications for these CQAs remain unchanged
- The values of the predicted CQAs are not used for quality release (no model-based or RTRT)

+

Model deployment:

- The model provides an optimized target for a critical process parameter cell culture duration within these ranges
- Via open loop control (SME oversight and intervention)



Case Study 2 – Control Strategy & Context of Use

Operational Mode

Open-loop control with human Subject Matter Expert (SME) oversight

Guardrails

- Model suggests targets only within already registered/validated ranges
- Predicted values are not used for product release; separate analytical QC release testing for acidic variants is retained
- Implementation: Planned post-approval implementation for a commercial product

Data

Built using both small-scale development and commercial-scale batch data

Case Study 1 – Regulatory Assessment & Filing Category

Risk Profile: Low due to **low decision consequence** and **low model influence**

Decision Consequence

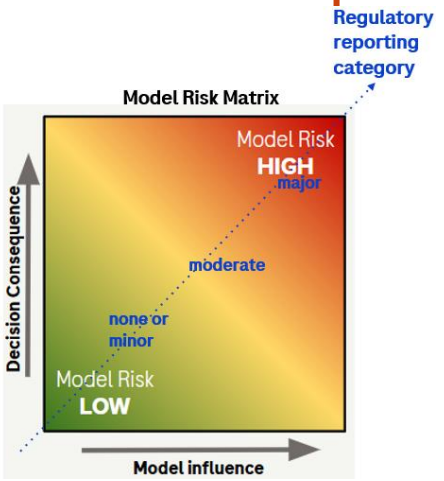
The model optimizes harvest time (CPP, acceptable range 13-15d), impacting IEC acidic variants (CQA). While failure could negatively affect CQA, the model output is within the registered 13 -15 day range, and actual harvest is primarily defined by subsequent process readiness.

Model Influence

Acidic variants are tested at release. The model output is not the sole decision factor; the system is open-loop with human intervention. The output can be used within the registered timeframe, but its use is not mandatory.

Filing Category: Assessed as **not regulatory relevant** and managed solely under the **Pharmaceutical Quality System (PQS)**

- ✓Model output is integral to the control strategy
- ✓Decision consequence: low
  Model influence: low
- ✓Model output has potential to affect a critical quality attribute (cQA), but it is limited by already existing, validated, and registered limits.
  There are other measurements in place, so it won't go outside the registered limits.



Case Study 2 - DL supported Automated Visual Inspection

Case Study 2 – DL supported Automated Visual Optical Inspection

Objective

To use DL in AIM to improve detection and categorization in critical, major, and minor defects in finished drug products with the aim to

- Increase Specificity and Reduce False Rejection
- Increase efficiency

Implementation

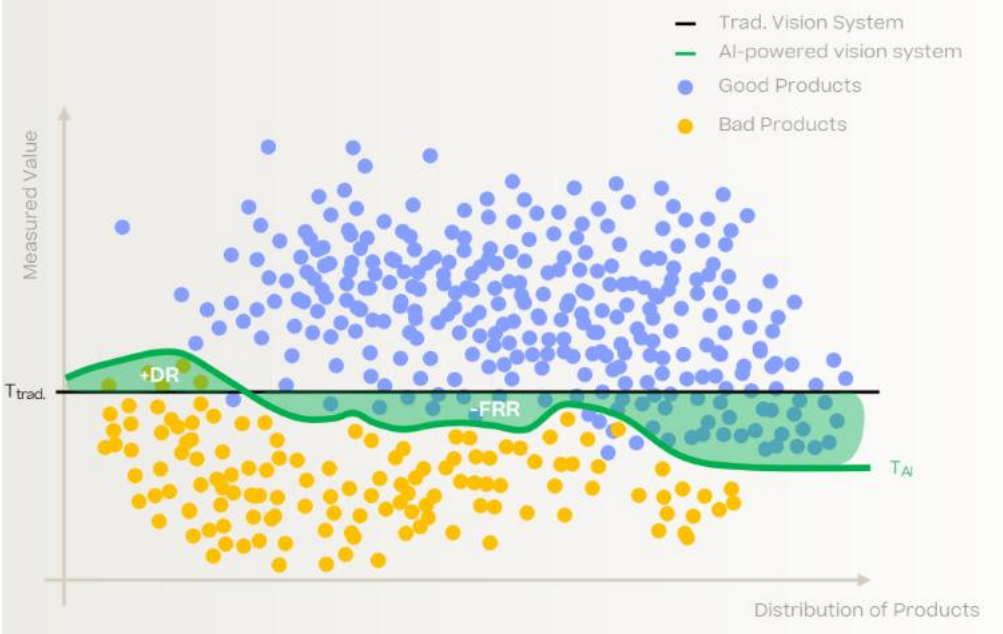
Planned mostly post-approval

Context

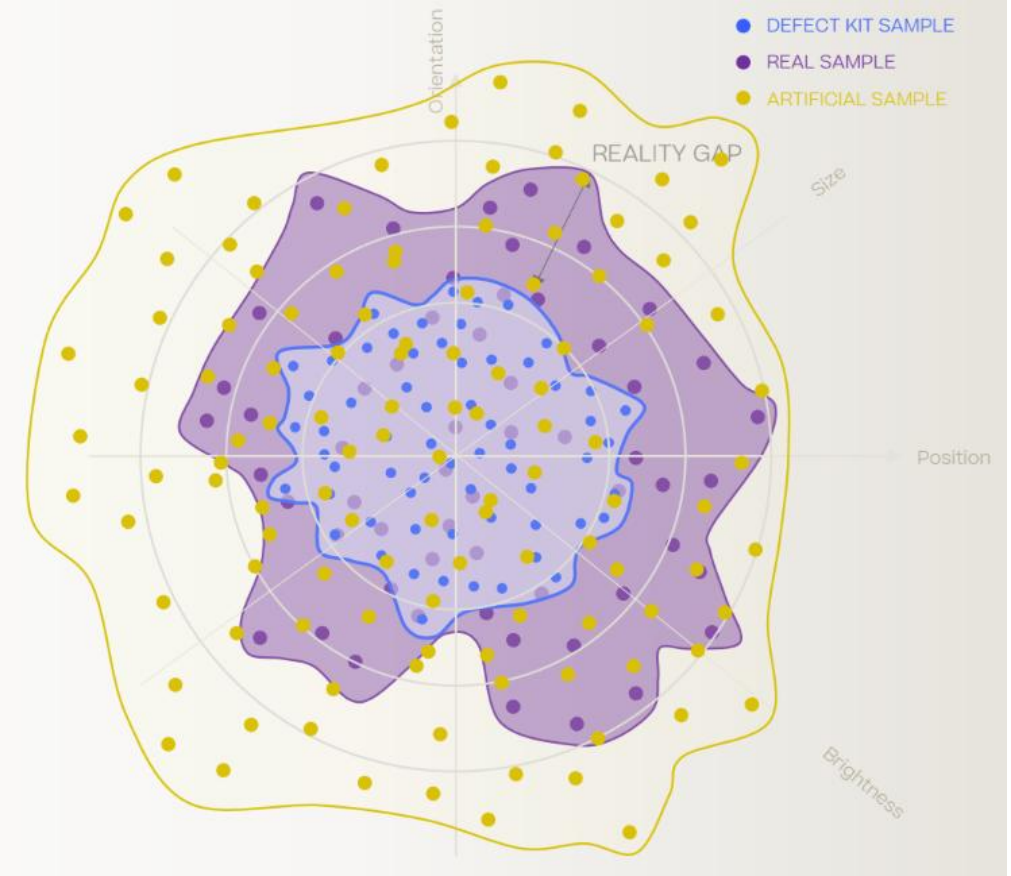
- Regulatory Requirement: 100% in-process inspection IPC) of parenteral products – followed by a lab-based Acceptable Quality Limit (AQL) test of a subset of samples
- AQL testing is integrated in the USP monograph <790> for the US;
- Manual (human operator) based visual inspection is well established, however, slow
- Automated visual inspection with «conventional algorithms» often has a high false reject rate
- Deep Learning applied in the following case study: Deployment of locked model (no autonomous updating – although possible option in the future)

Case Study 2 – What AI Can Do

Reduction of False Positive Detection



AI offers the possibility to introduce non-linear decision making in the inspection process



As defect kits are limited in representativeness, the original data is extended by artificially generated data to increase variability.

Case Study 2 – Deployment Scenarios, Different CoU & Filing Impact

AQL testing retained as registered & DL locked model

Scenario A	Scenario B	Scenario C (Grey Channel)	Scenario D (RTRT)
			
Replacing existing AIM with DL supported AIM for IPC	Replacing manual inspection with DL supported AIM for IPC	Replacing manual re-inspection of 'grey channel» units that high speed AIMs could not definitly classify	(Real-Time) Release Testing: replacing manual AQL/release testing with DL supported AIM
Reporting category			
minor change / not reportable* (or subject to internal GMP/PQS only) for standard like-for-like changes	**≥ Moderate**	**≥ Moderate**	**major**

Model influence/CoU increases to high

*discussed with EMA QIG, Nov 2023

Case Study 2 – Summary Assessment for Low Model Influence

Example for Risk Profile Low
Scenario A_Replacing existing AIM with DL supported AIM for IPC

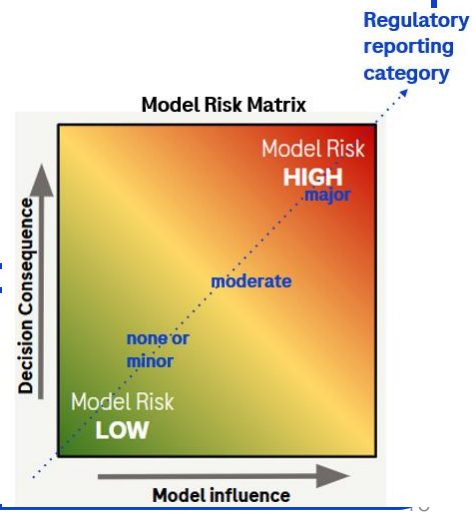
Decision Consequence **low**

- No changes to Internal procedure *"Visual Inspection for Parenteral Drug Products"* are required for initial implementation
- + additional loop for DL
- Locked model is qualified as for conventional AIM (DL is not "open or autonomous")
- => (re-)qualification and (re-)validation approach will be the same as for other AIMs, and non-inferiority to manual inspection to be demonstrated

Example for Risk Profile Medium
Scenario B_Replacing manual inspection with DL supported AIM for IPC

Decision Consequence **medium or high**

- No changes to Internal procedure *"Visual Inspection for Parenteral Drug Products"* are required for initial implementation
- + Change from manual to automated visual inspection
- + additional loop for DL



Model Influence **low**

- Data not used for release decision but IPC only
- Final decision with AQL/release or stability testing (with no change to registered status)

Case Study 2 – Summary Assessment for High Model Influence

Example for Risk Profile High
Scenario D_Replacing manual AQL/release testing with DL supported AIM

Decision Consequence **medium or high**

- No changes to Internal procedure *"Visual Inspection for Parenteral Drug Products"* are required for initial implementation
- + Change from manual to automated visual inspection
- + additional loop for DL

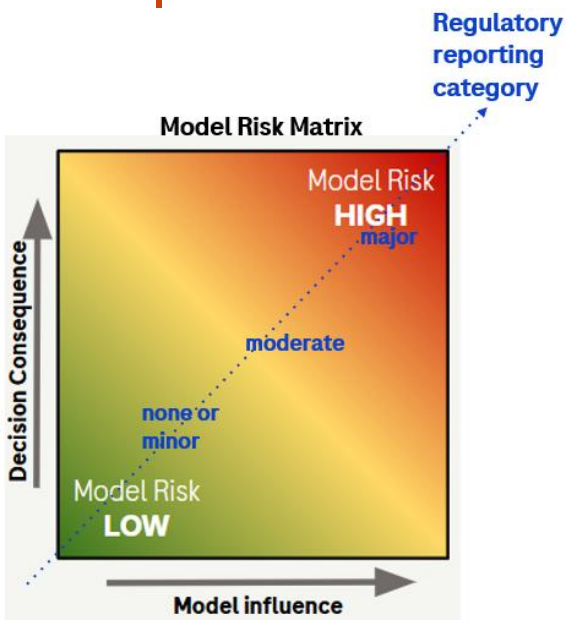
Model Influence **high**

- Data used for release decision, final QC

Reporting Categories for different examples:

Complete range – from not reportable to major, depending on

- the deployment,
- prior knowledge,
- country



Conclusion and Key Takeaways

Conclusion & Key Takeaways

Context is King

The Context of Use (COU) is fundamental determinant of model risk and subsequent regulatory requirements.

Model risk (Decision Consequence x Model Influence) dictates reporting category, dossier depth, and maintenance rigor.

Optimization versus Control Strategy

Low-Risk (Optimization): Managed within the PQS to enable fast implementation and foster innovation without approval delays;

High-Risk (e.g. Release): Included in the dossier with appropriate level of details.

Lifecycle is Critical

Robust PQS oversight, monitoring and structured workflow is mandatory to ensure models remain fit for purpose and to detect data or concept drift.

A Change Management Protocol can be utilized for efficient (low registration burden), transparent and pre-approved management of iterative model improvements.

Early Alignment is Essential

Early engagement with the FDA ETP, or EMA QIG or ITF or Parallel Scientific Advice is critical to align on COU and documentation rigor before formal filing.


MODEL OVERSIGHT: NAVIGATING THE ROADS OF AI REGULATION IN PHARMA
POS
POS
POS
the
dossier

THANK YOU

Doing now what patients need next

Artificial Intelligence (AI):
The science and engineering of making intelligent machines

Enables machines to simulate human intelligence - processing data, recognizing patterns, and making decisions to perform complex tasks efficiently.

Machine Learning (ML):
A major approach to realize AI

Subset of AI where algorithms learn from data to improve decision-making and predictions without explicit programming.

Deep Learning (DL):
A branch of ML

Advanced type of machine learning that uses neural networks with multiple layers to analyze complex data patterns and improve accuracy in tasks like image recognition and natural language processing.

Generative AI (GenAI)
Includes LLMs/SLMs

Subset of deep learning that uses existing structured & unstructured data to generate new content by learning patterns from existing data.