June 25th 2026

Digital CMC Transformation Driven by Modelling and Agentic AI

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CMC Advocacy and Policy Director – Global Regulatory Affairs

gsk.com

Overview

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Digital innovation in the development and manufacture

2

Process Development and Controls

3

Models, AI and GMP

4

Generative AI and Structure Data

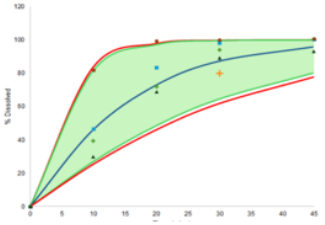
5

Conclusions

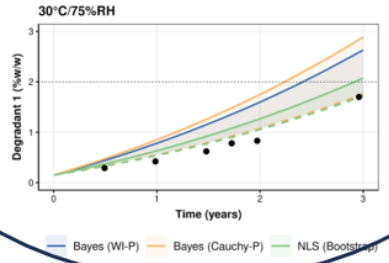
Digital innovation in the development and manufacture

Models in Pharmaceutical Development and Manufacture

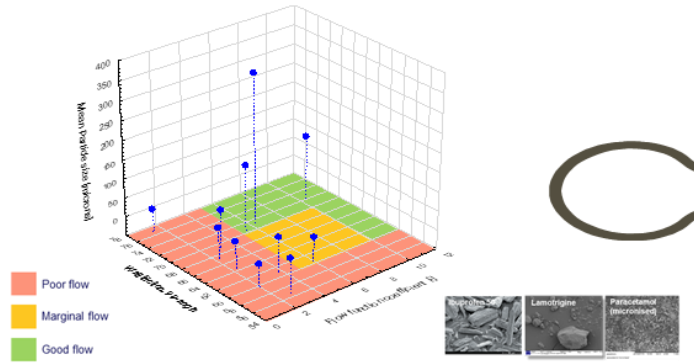
Clinically relevant specifications eg dissolution safe space supported by PBBM



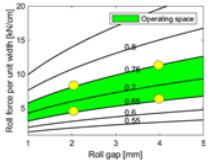
Shelf life: eg model-based justification of shelf life

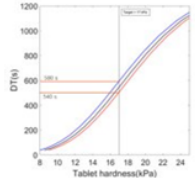


1 Predict First Product and Process Design

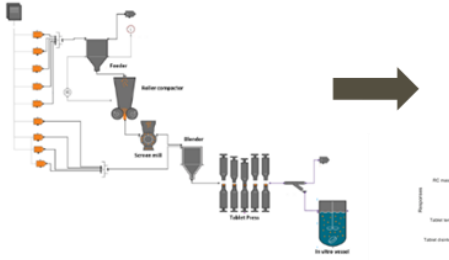


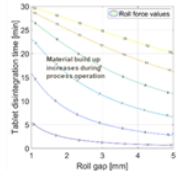
2 *In Silico* Design Space Identification

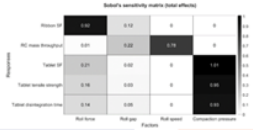




3 Model Driven Control Strategy Development





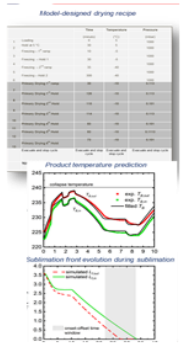


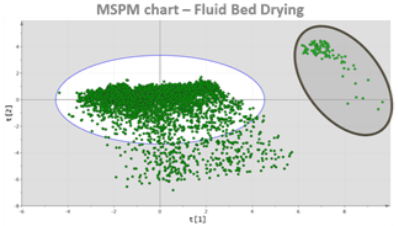
Sobol's sensitivity index (disintegration time)= 0.05

Suggested scoring: 4 (slightly severe)

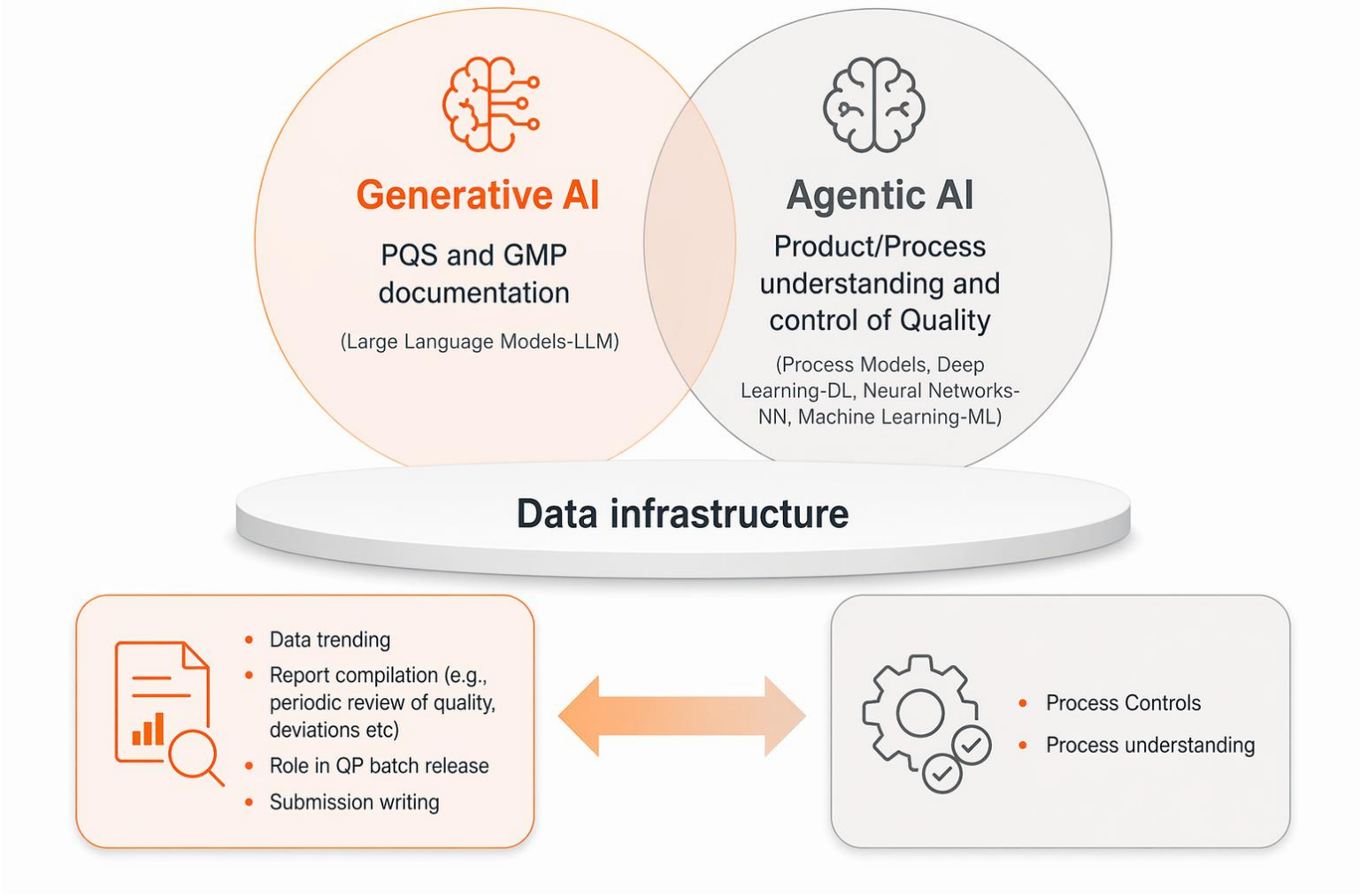
Suggested knowledge scoring: Good

4 Model Based Control Verification and Predictive Lifecycle Management





AI in CMC Development & Manufacturing



What regulatory framework is needed for Digital Innovation?

Guidance on Process Models and AI

Regulatory body - Organization	Links to recent released guidance
ICH	2011 Q8-10 Points to Consider (PTC) document (section 5 Role of models in QbD) 2023 Q13 Continuous Manufacturing, section 3.17 Process Models 2024 M15 Principles for Model Informed Drug Development 2025 FDA ICH Reflection Paper on advanced manufacturing
ASME*	2018 VVUQ 40–VVUQ in Computational Modeling of Medical Devices (In preparation) VVUQ 80–VVUQ in Computational Modeling of Pharmaceutical Products
EMA	2024 Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle 2024 EMA QIG Preliminary Considerations on Process Models 2025 Revised Annex 11 – Computerised Systems and New GMP Annex 22 – Artificial intelligence
FDA	FDA Frame 2023 Assessing the Credibility of Computational Modelling and Simulation in Medical Device Submissions 2023 Artificial Intelligence in Drug Manufacturing and Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products 2025 FDA Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products
Japan-PMDA	Japan AMED Working Group on Process Models

* **ASME:** American Society of Mechanical Engineers

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Why is Model Risk Determination Important?

Start with defining overall **context of use** of the model

- What type of product/process?
- What problem to solve?
- What types of models?

Then, define Model Risk

- Considering **Model Influence** (eg the contribution of the model to the control strategy)
- **Decision consequence** (eg the significance of an adverse outcome resulting from an incorrect decision based on the model, considering the control strategy)

Next, determine the **credibility** requirements to address the risk

- Match to planned role in the control strategy
- Determines requirements for **registered detail, and supporting information, development, validation/verification...**

Approvability/Confidence

Model/AI Risk Evaluation Frameworks

ICH harmonisation for better health

ICH QUALITY IMPLEMENTATION WORKING GROUP
POINTS TO CONSIDER (R2)

ICH-Endorsed Guide for
ICH Q8/Q9/Q10 Implementation

Document date: 6 December 2011

I. *Low-Impact Models:*
These models are typically used to support product and/or process development (e.g., formulation optimisation).

II. *Medium-Impact Models:*
Such models can be useful in assuring quality of the product but are not the sole indicators of product quality (e.g., most design space models, many in-process controls).

III. *High-Impact Models:*
A model can be considered high-impact if prediction from the model is a significant indicator of quality of the product (e.g., a chemometric model for product assay, a surrogate model for dissolution).

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SCIENCE MEDICINES HEALTH

22 February 2024
EMA/90634/2024

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Preliminary QIG Considerations regarding Pharmaceutical Process Models

Q3. What data is expected to be included in the dossier in terms of model validation?

Risk	Example	Dossier location	Dossier requirements (see also question Q2)
Low	Process development, e.g. used to develop process understanding. Process optimisation (w/o change to registered process details). Mechanistic model used to speed up bioprocess scale-up/down. Digital Twin in shadow mode. Support batch release decisions based on QA predictions.	Dossier sections S.2.6/P.2.3 and S.2/P.3, as appropriate.	High level description of the model intent, type of model and how it is used. Manufacturing process validation data as described in the process validation guidelines.[4,5]
Medium	Process design (change to unit operation principle or setting of in-process control limits). RTD model in combination with in-line NIR process control. Support batch release decisions based on CQA predictions but used in combination with PAT and release testing.	Dossier sections S.2.6/P.2.3 and S.2/P.3, as appropriate.	Detailed description of the model intent, type of model, how model is used and model operation, model assumptions, type of data used and model validation summary. Manufacturing process validation data as described in the process validation guidelines.[4,5]
High	RTD model w/o other related in-process measurement. Real-time release testing (reduced release testing).	Dossier sections S.2.6/P.2.3, S.2/P.3 and S.4/P.5, as appropriate.	As for medium risk above, plus model validation report (training/ validation/ test datasets, prediction metrics acceptance criteria, model validity space, *etc.*).

FDA U.S. FOOD & DRUG ADMINISTRATION

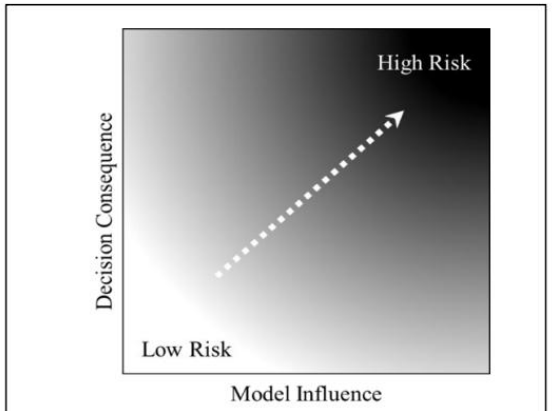

Figure 1. Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for decision consequence and model influence are independently determined.

FDA Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products

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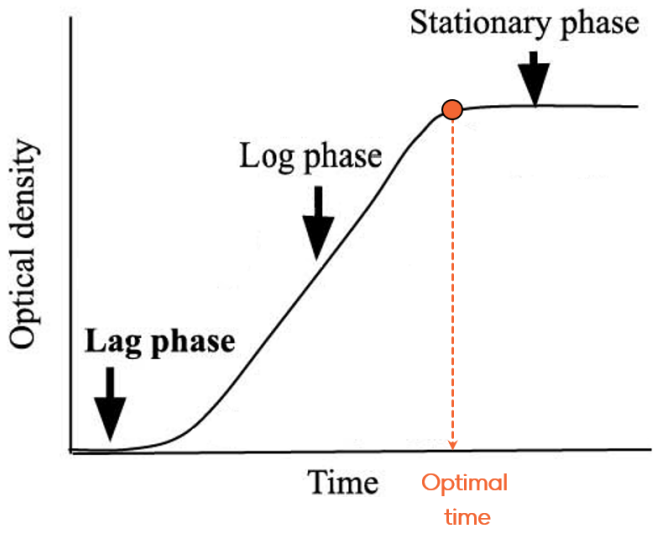
Process Development and Controls

Fermentation Outer Membrane Vesicles (OMV) – Digital Twin

Background:

- To maximize the final quantity of Antigen, there is an optimal time to stop the step of cell culture
- Criterion to stop cell growth: ΔOD < 5%/h
- Variable accuracy on OD measurements

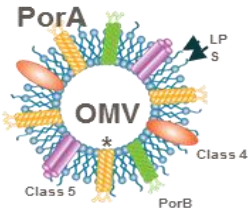


Lag phase: This is the initial phase where cells are adapting to the new environment

Log phase: Cells enter a period of rapid growth and division

Stationary phase: As nutrients become depleted and waste products accumulate

Optimal time to stop the step of cell culture:
Transition between Log phase and Stationary phase
➔ Maximize cell (and thus Antigen yield)
➔ Prevent loss of production time



*Outer Membrane Vesicles (OMV) are extracted from the bacterial membrane of *Neisseria meningitidis* serogroup B

Fermentation Outer Membrane Vesicles (OMV) – Digital Twin

Low risk model – Internal change - PQS

OMV Fermentation Modelling & Digital twin:

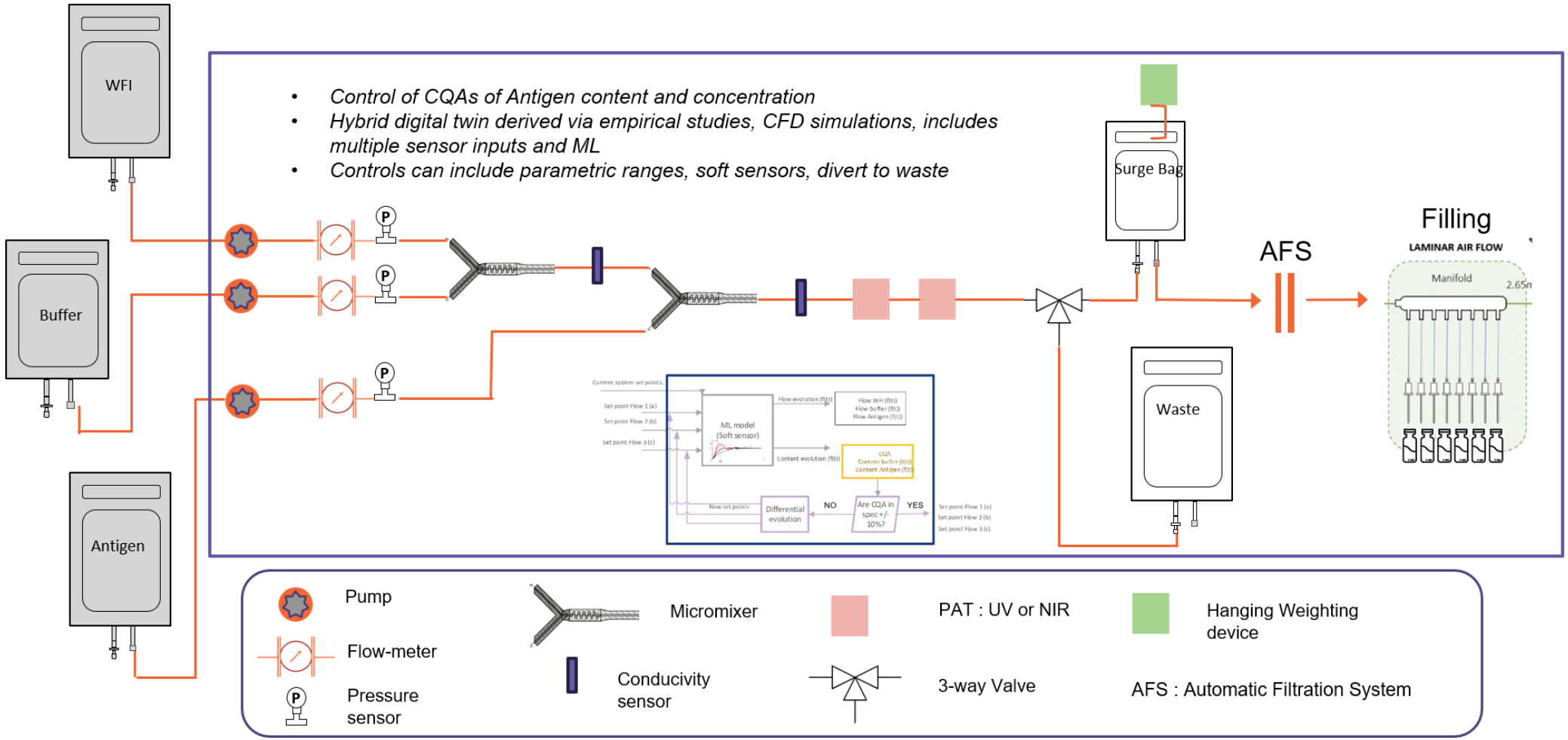
- Improvement step: Implementation of regression curve (near future)
  - To smooth out errors on OD measurements and increase batch-to-batch consistency
- Optimization step: Implementation of Digital Twin (next step)
  - To estimates the correct OD and increase the yield by changing fermentation stop criterion

Key benefits:

- Improved robustness, batch-to-batch consistency and yield

Continuous Sterile Formufilling – Digital Twin

Medium/High risk model



* 1st Quality Innovation Listen and Learn Focus Group (LLFG) 13/03/2023

EMA QIG Preliminary Considerations on Process Models

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SCIENCE MEDICINES HEALTH

22 February 2024
EMA/90634/2024

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Preliminary QIG Considerations regarding Pharmaceutical Process Models

Q2. What data is expected in the dossier in terms of model description and scope?

The level of detail regarding the model development and its description in the regulatory submission is dependent on the intended use of the model, its role in the control strategy, and the risk to material quality. This forms the basis for defining the degree of justification, and the extent of description, in an application. Requirements are defined as a function of the model risk (see Table 1 in question Q3).

Q3. What data is expected to be included in the dossier in terms of model validation?

Risk	Example	Dossier location	Dossier requirements (see also question Q2)
Low	Process development, e.g. used to develop process understanding. Process optimisation (w/o change to registered process details). Mechanistic model used to speed up bioprocess scale-up/down. Digital Twin in shadow mode. Support batch release decisions based on QA predictions.	Dossier sections S.2.6/P.2.3 and S.2/P.3, as appropriate.	High level description of the model intent, type of model and how it is used. Manufacturing process validation data as described in the process validation guidelines.[4,5]
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FDA Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products

Applicable to all model development (including AI/ML)

1. **Question of Interest**
2. **Context of Use**
3. **Model Risk**
4. **Model Credibility**
   - Model selection
   - Model Development
   - Verification/validation

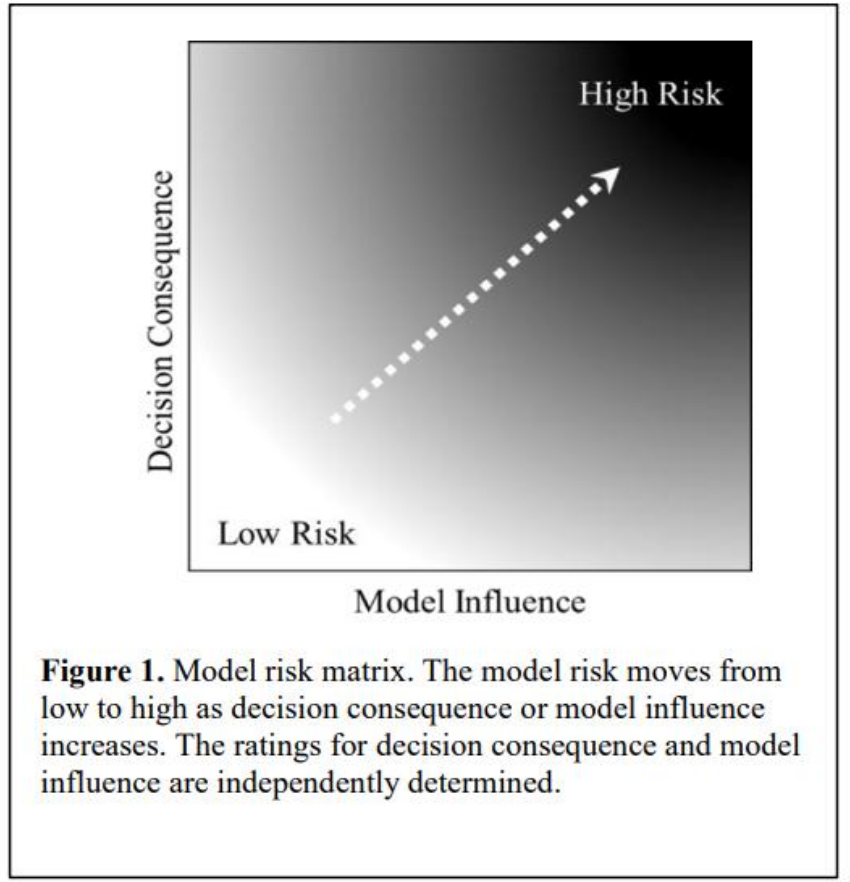


Figure 1. Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for decision consequence and model influence are independently determined.

Process Model Development and Deployment

Strategy for initial market supply

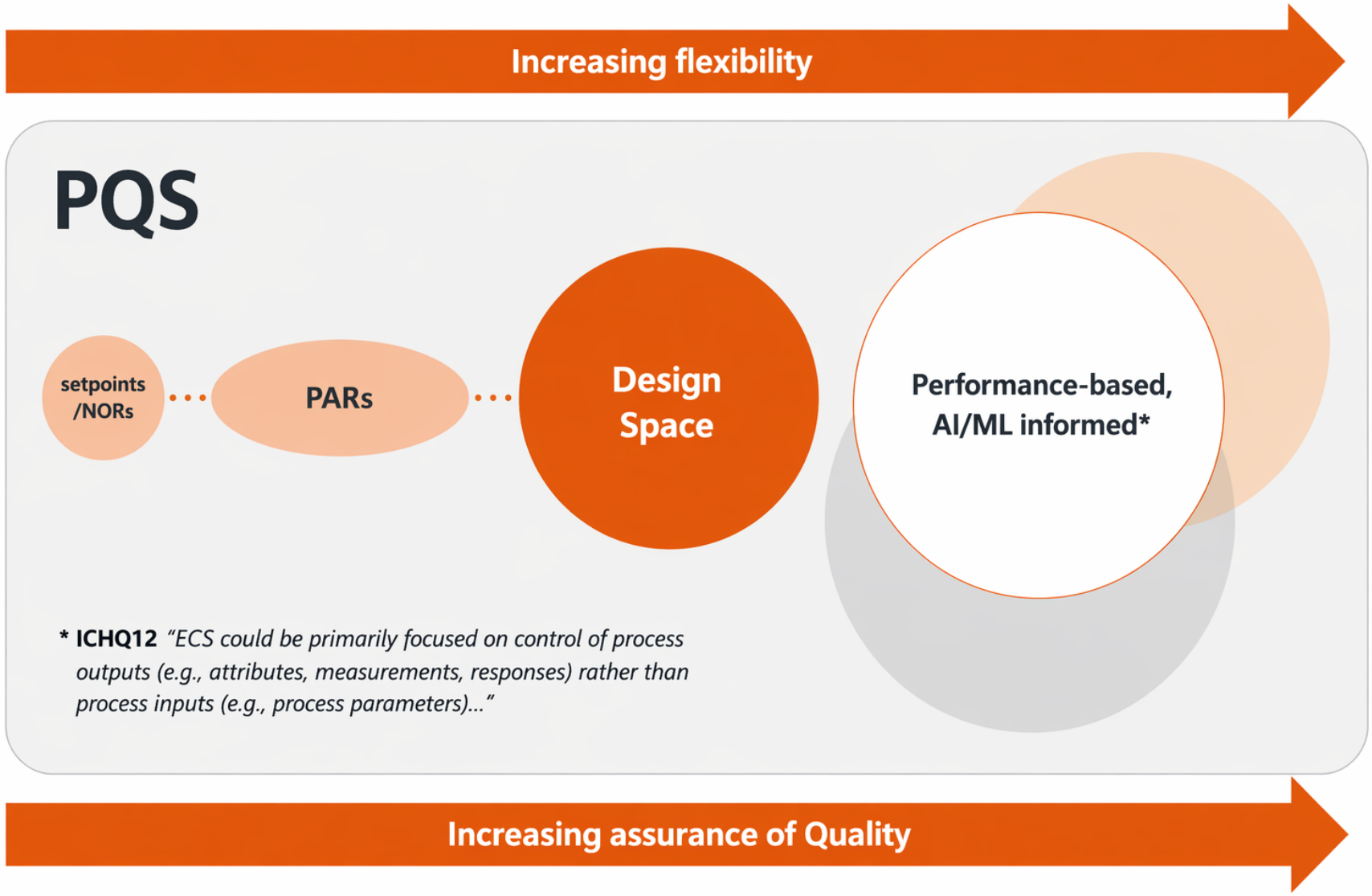
- Model active during manufacture to **control the process within the design space**
  - Process boundaries defined based on the model and then experimentally verified
  - Control strategy unchanged (CQAs tested as part of batch release)
- **Model performance demonstrated in development and PPQ**, (showing superiority of model-based control over classical fixed parametric controls)
  - Data from PPQ and subsequent CPV shows the process is in a state of control
- Model validation should not be required, and only limited data on the (low/medium impact/risk) model required in the dossier

Future State

- Further model data provided in the dossier (CQI/ECs)
- Increased model verification/validation
- Reduced end-product testing
- Simplified PPQ?
- Performance-based control strategy?

Framework will be required to ensure that changes to models can be managed under the site PQS without requiring prior approval

Evolution of Process Model-based control



Models, AI and GMP

GMP Requirements for Airflow & Airborn Particles

Source: ISPE Baseline Guide: Sterile Product Manufacturing Facilities (Third Edition)

Reference	Description			Classification					
ISPE Sterile Product Baseline® Guide (Third Edition)	Harmonized Designations			ISO 5/ Grade A	ISO 6	ISO 7/ Grade B	ISO 8/ Grade C	Grade D	CNC [Note 1]
US FDA [3]	ISO Designation			ISO 5	ISO 6	ISO 7	ISO 8	N/A [Note 2]	N/A
	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/ft³	100	1,000	10,000	100,000	Not defined	Not defined
			0.5 µm particle/m³	3,520	35,200	352,000	3,520,000	Not defined	Not defined
EU [1] and PIC/S [9]	Descriptive Grade			Grade A	N/A [Note 4]	Grade B	Grade C	Grade D	Grade D
	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	35,200	352,000	3,520,000	Not defined	Not defined
			5.0 µm particle/m³	20 [Note 3]	Not defined	2,900	29,000	Not defined	Not defined
	At Rest	Maximum no. particles permitted ≥ the stated size	0.5 µm particle/m³	3,520	Not defined	3,520	352,000	3,520,000	Not defined
			5.0 µm particle/m³	20 [Note 3]	Not defined	29	2,900	29,000	N/A
US FDA [3], EU [1], and PIC/S [9]	In Operation	Microbiological Active Air Action Limits, CFU/m³ [Note 5]		< 1	7	10	100	200	Not defined

EMA - Eudralex Annex 1 (2022):

- "The "clean Up" period (guidance value of less than 20 minutes) should be determined during *the qualification of the rooms…"*

FDA - Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - cGMP (2004) *:*

- "*Air change rate is another important cleanroom design parameter. For Class 100 000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10 000 and class 100 areas*"

China GMP Annex

- *''The particulate conditions shown in the table for the "at rest" state should be obtained in the unmanned state after a short cleanup period of 15-20 minutes (guidance value), upon completion of operations.*

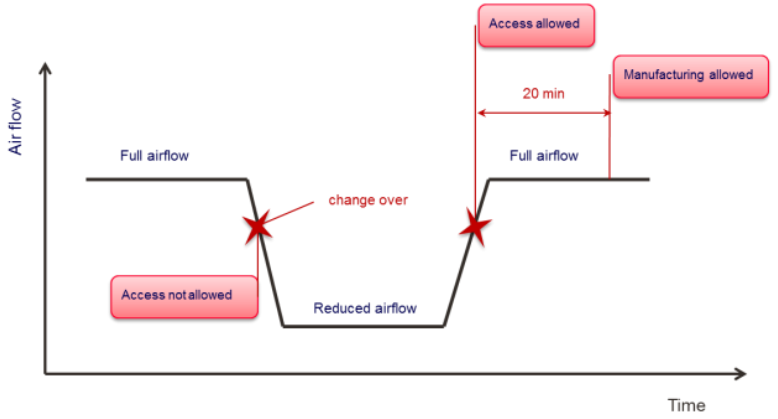
Adaptive Airflow

Past: Traditional approach

HVAC design for “full airflow” all the time

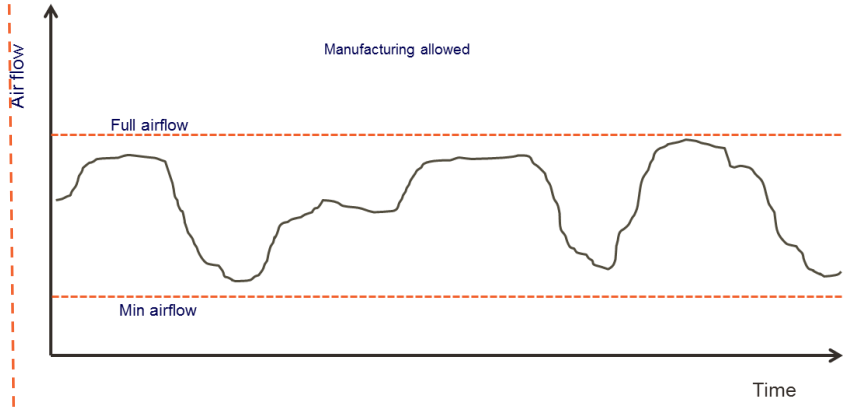
Today: Airflow Reduction Mode

HVAC design for reduced airflow during non production hours

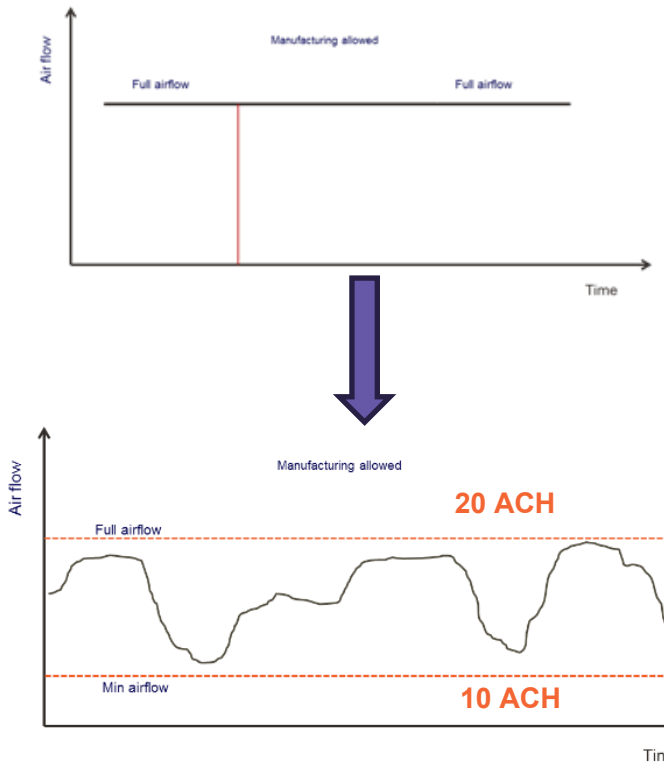


Future: Adaptive Airflow

HVAC design for dynamic airflow based on particle level



Adaptive Airflow technology



Existing

BMS (SIEMENS)
Building Management System

- Airflow
- Pressure control
- Temperature & RH
- Energy counter -Elec

New

New equipment

- Controller connected with particle counters

AHU
Air Handling Unit

VAV
Variable Air Volume

CLEANROOM

New
Particle counter

Mobile Monitoring

New
Particle counter

VAV
Variable Air Volume

HVAC – Heating, Ventilation, and Air Conditioning

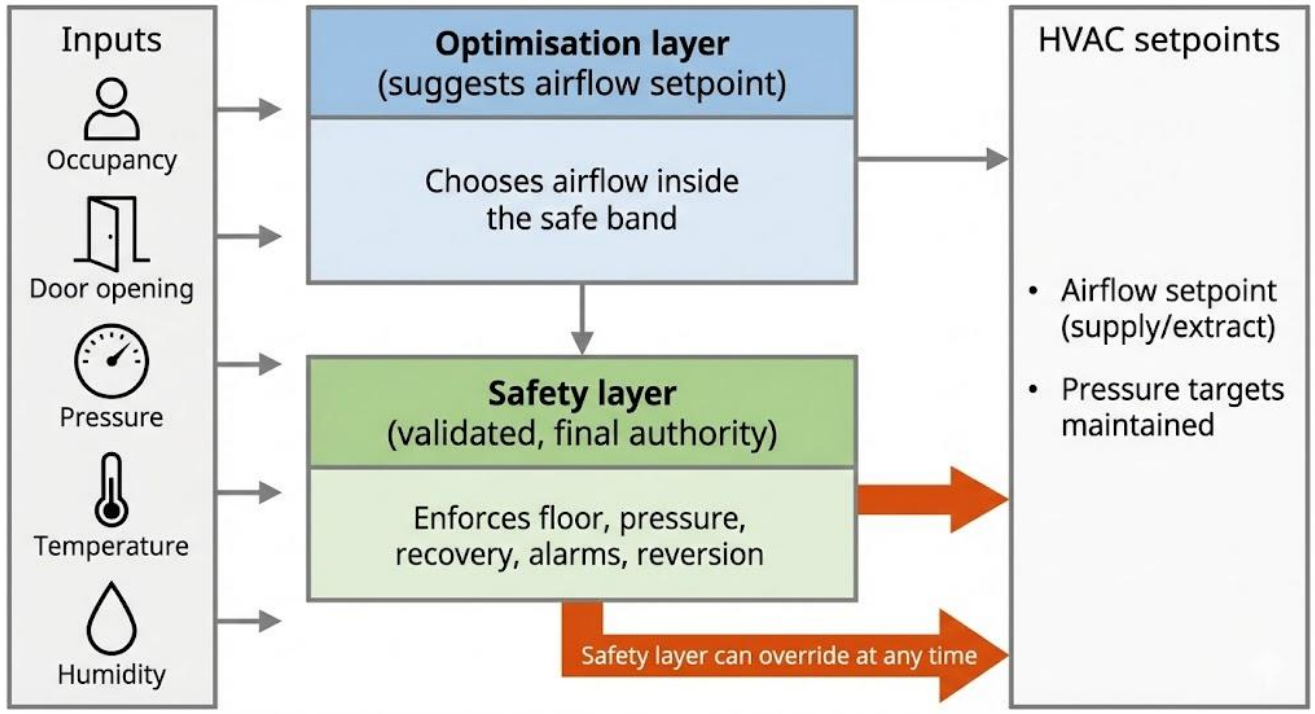
‘Digital Twin + Learning’ Controller That Chooses The Lowest Safe Airflow

What is genuinely new vs “adaptive airflow V1”:

Not just “react to particles and ramp up”

It is **look-ahead control** that uses:

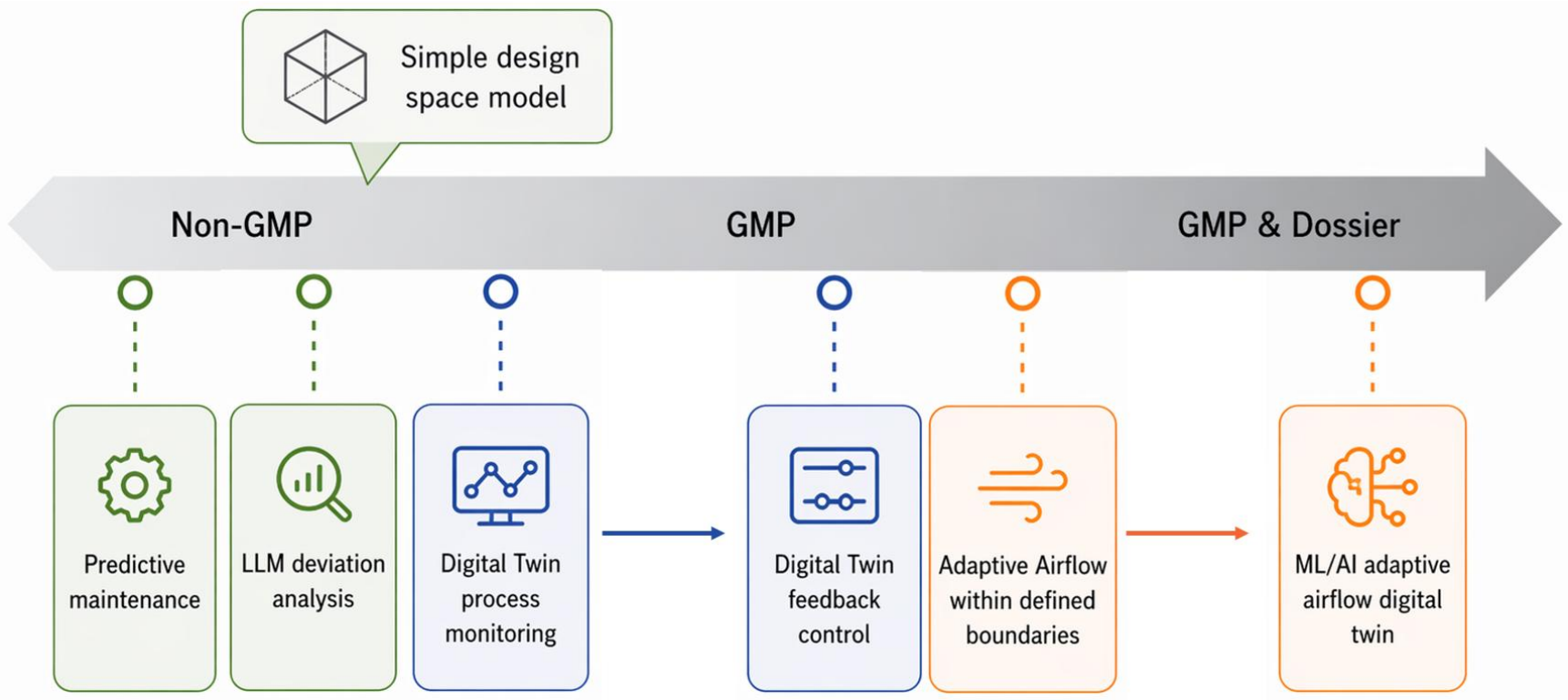
- A **digital twin** (a simple physics-based model of the room/AHU/pressure network), and
- A **learning model** to forecast disturbances (people + doors + expected particle generation)
- Plus, an **uncertainty estimate** (“how sure are we?”). When not sure → it chooses the safer option



Adaptive Airflow

- Using dynamic modulation of the airflow in real-time (focused on Grade C (ISO 8) and Grade D facilities) can reduce HVAC energy use by 30-40%
- When **recovery time**, **pressure control**, and **particle performance** remain within qualified limits, the **airflow setpoint** can become a **managed variable** rather than a fixed constant.
- The more **sophisticated** the model, the **greater the energy saving**
- The more **sophisticated** the model, the **greater the need for qualification and control**

GMP: A framework to de risk AI and ML

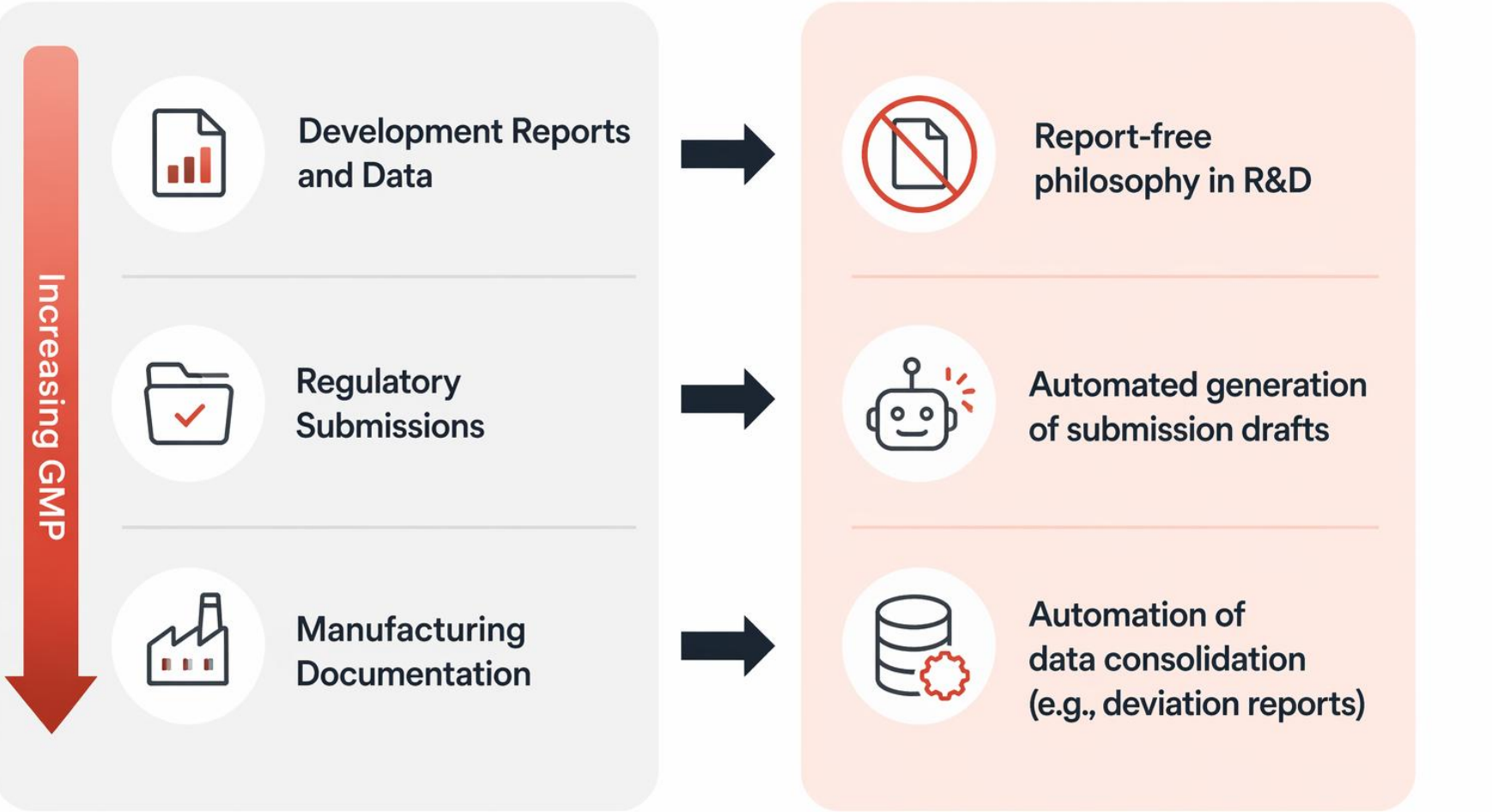


Example characteristics of GMP which derisk models and Agentic AI

- Pharmaceutical Quality System (PQS)
- CPV and periodic product review (model performance)
- Inspections
- Humans in the loop (e.g., batch release including QP)

Generative AI and Structure Data

Generative AI using LLM



ICH: Document-Centric to Data-Centric Submissions

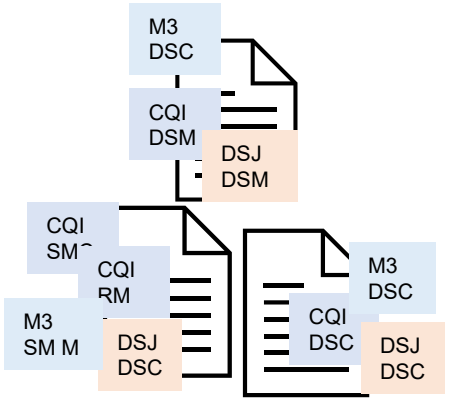
ICH M4Q (R2)

Paves the way for **data centric submissions** by defining and organizing product and manufacturing information in a medicinal product dossier.

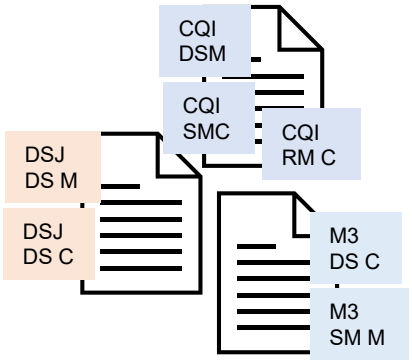
ICH M16 (Structured Product Quality Submissions)

Aim to develop/**adopt global standards for data content and structure** in submitting product quality information in a dossier to facilitate regulatory assessment and efficient communication between the applicants and regulators.

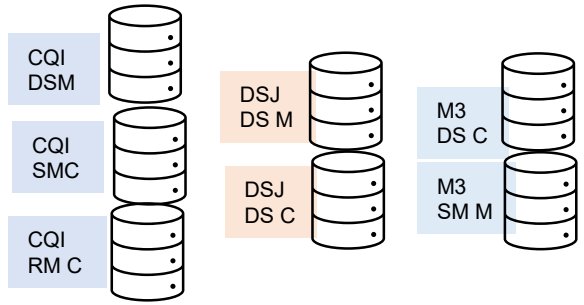
ICH M4Q(R1) - Information organized in a sequential narrative way with different structure across chapters



ICH M4Q(R2) - Information organized in a logical and standardized way across chapters

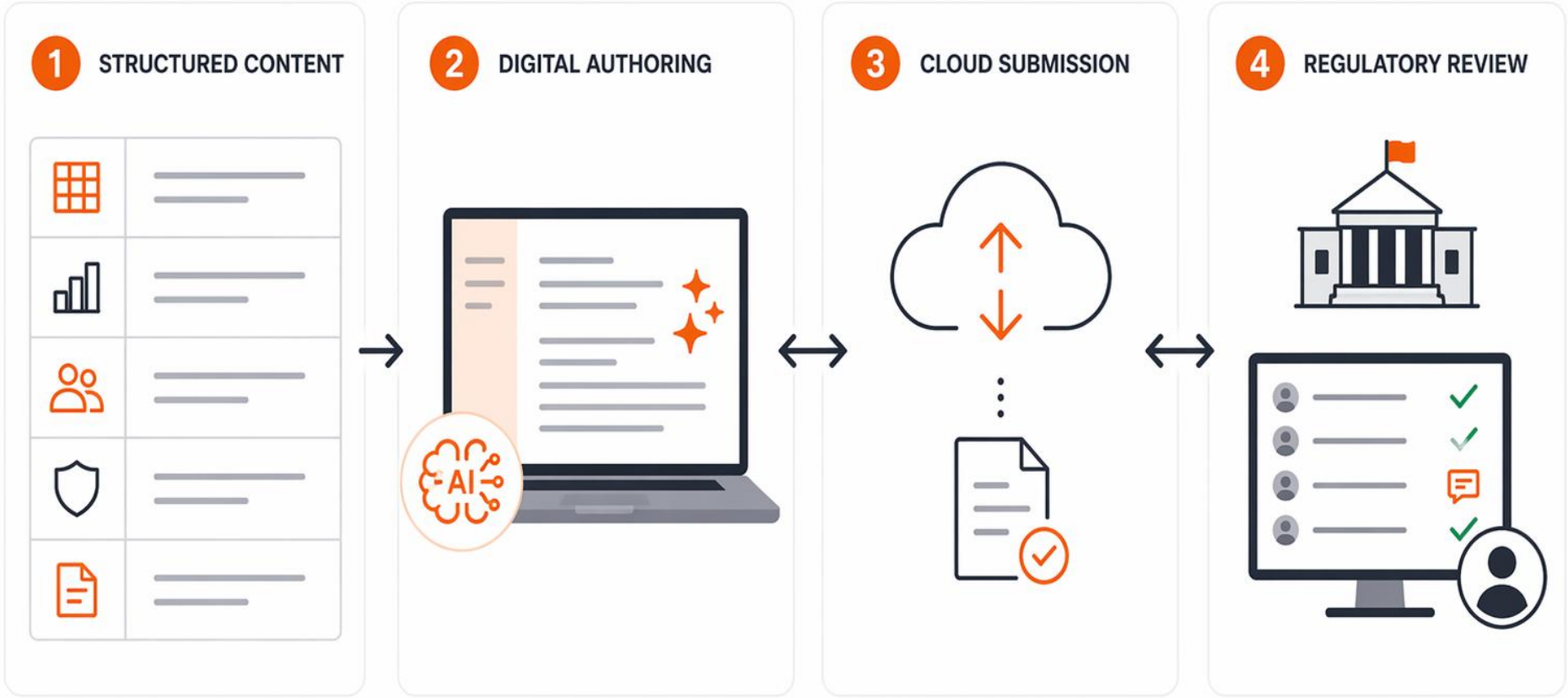


ICH M16- Data models defined for each piece of information. Data base submissions can replace document



D Description; **M** Manufacture; **C** Control; **S** Storage; **CQI**= Core quality information; **DSJ**= Development Summary and Justification
DS =Drug substance; **SM**= Starting material; **RM**= Raw material; **CQI DS M** equals = Core quality information, Drug substance Material

Generative AI* - Assisted Submissions



* AI generated picture

Evolution of GMPs

GMP Annexe For AI

Stakeholders' Consultation on EudraLex Volume 4 - Good Manufacturing Practice Guidelines: Chapter 4, Annex 11 and New Annex 22

Revised Annex 11 establishes enhanced requirements for computerised systems.

New Annex 22 addresses general principles for the development of AI in manufacturing, aligning with expectations under the Pharmaceutical Quality System and potentially influencing dossier content.

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New GMP Annex 22

Annex 22: Artificial Intelligence

Reasons for changes: Not applicable (new annex).

Document map

1. Scope
2. Principles
3. Intended Use
4. Acceptance Criteria
5. Test Data
6. Test Data Independency
7. Test Execution
8. Explainability
9. Confidence
10. Operation

Glossary

16 The document applies to models with a deterministic output which, when given identical inputs, provide
17 identical outputs. Models with a probabilistic output which, when given identical inputs, might not
18 provide identical outputs are not covered by this document and should not be used in critical GMP
19 applications.

20 Following the above, the document does not apply to Generative AI and Large Language Models
21 (LLM), and such models should not be used in critical GMP applications. If used in non-critical GMP
22 applications, which do not have direct impact on patient safety, product quality or data integrity,
23 personnel with adequate qualification and training should always be responsible for ensuring that the
24 outputs from such models are suitable for the intended use, i.e. a human-in-the-loop (HITL) and the
25 principles described in this document may be considered where applicable.

87 **6. Test Data Independency**

88 6.1. *Independence*. Effective measures consisting of technical and/or procedural controls should
89 be implemented to ensure the independency of test data, i.e. that data which will be used to
90 test a model, is not used during development, training or validation of the model. This may
91 be by capturing test data only after completion of training and validation, or by splitting test
92 data from a complete pool of data before training has started.

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New GMP Annex 22 - June 30th 2026: EMA workshop

June 30th 2026: EMA workshop

- EU GMP Annex 22 on Artificial Intelligence sets requirements for selecting, validating, monitoring, and controlling AI systems used in pharmaceutical manufacturing.
- The annex focuses on:
  - Machine learning (AI/ML) models which have obtained their functionality through training with data, rather than being explicitly programmed. Models may consist of several individual models, each automating specific process steps in GMP.
  - Static AI models that do not keep learning after deployment, supporting reproducibility and control
  - Models with a deterministic output which, when given identical inputs, provide identical outputs.
  - "The document does not apply to Generative AI and Large Language Models (LLM), and such models should not be used in critical GMP applications".
- It also complements Annex 11 on computerised systems
- *"Final publication is expected in 2026, and manufacturers are encouraged to prepare now".*

Current Draft Annex 22

Conclusions

AI in CMC Development & Manufacturing

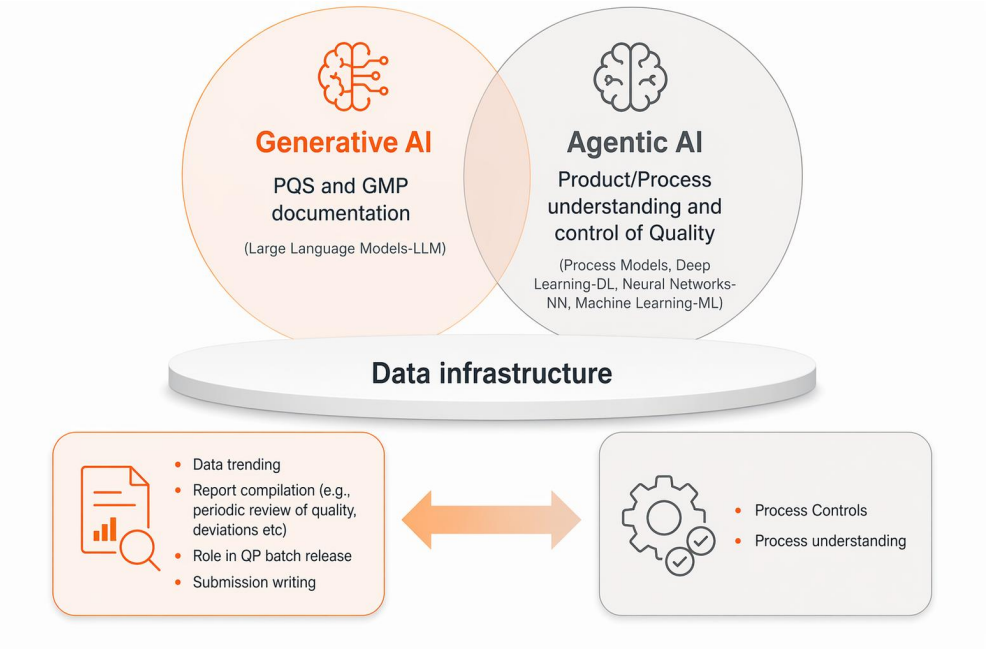
Agentic AI and Models

- A risk evaluation framework is key
- The guardrails of GMP can de-risk even complex model & AI controls

Generative AI

- LLMs can transform how data and knowledge are handled in dossiers, development, manufacturing

Data infrastructure will be critical (ICH M16, ISO CMC….)



2026 IFPMA Paper

Real-world applications of AI and ML in manufacturing

AI and ML can be applied across various processes and by different functions within pharmaceutical development and manufacturing, demonstrating tangible benefits. Examples of potential applications include, but are not limited to:

ML models for process prediction or control (digital twins of manufacturing processes)

ML models are employed to predict reality with proposed outcomes (for example, predicting the yield of a monoclonal antibody manufacturing process). These methodologies involve creating so-called "digital twins," which are digital models of an entire manufacturing process or of an individual step in a process. The "digital twin" translates historical experience or designated process development data with the same or similar product or their manufacturing process into actionable information. Digital twins can be used either as part of the control system or outside the established control system (for improving planning and scheduling of production runs), with a different resulting level of risk.

Deep learning for automated visual inspection (AVI)

Deep learning algorithms have been utilized to support the quality assurance process to comply with prior-established parenteral product specifications/ requirements. As an example, while 100% in-process visual inspection of all filled parenteral products is a regulatory requirement in some jurisdictions, the manual inspection by staff can create a bottleneck. Further, the use of conventional algorithms to support automated visual inspection often produces a significant number of false positives. Deep learning-powered algorithms and computer vision can help reduce false reject rates, minimize manual re-inspection, prevent delayed product release, and reduce the loss of product that comply with the required specifications.

Generative AI (GenAI) for text management

Beyond direct manufacturing operations, GenAI applications can help generate content proposals for regulatory required reports and summaries that could be used in regulatory dossiers, trend analysis, improving readability and accuracy in quality reporting, and enhancing knowledge management through advanced search and report generation in technical development. For this type of application, GenAI technologies will support the work of trained individuals (i.e. "Human in the Loop - HITL") and improve readability and accuracy in quality reporting while reducing the effort needed[1].

The evolving regulatory landscape

Many NRAs around the world are developing regulations and guidance on application of AI and are generally taking a risk-based approach to oversight of AI used in drug development and manufacturing. A key consideration is determining the level of detail that should be available for routine inspections versus what needs to be submitted in the regulatory dossier, an issue that is especially important for marketed products and management of post-approval changes.

Many NRAs including both the FDA (U.S. Food and Drug Administration) and the EMA (European Medicines Agency) show a strong and comparable level of regulating principles of the application of AI across the medical life cycle. Today, most NRAs published reflection papers and draft guidance for further discussions in this area.

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