Regulatory Considerations for Pharmaceutical Manufacturing Process Models

Ben Stevens

Disclaimer

Ben Stevens is a current employee of the GSK group of companies and holds shares in GSK.

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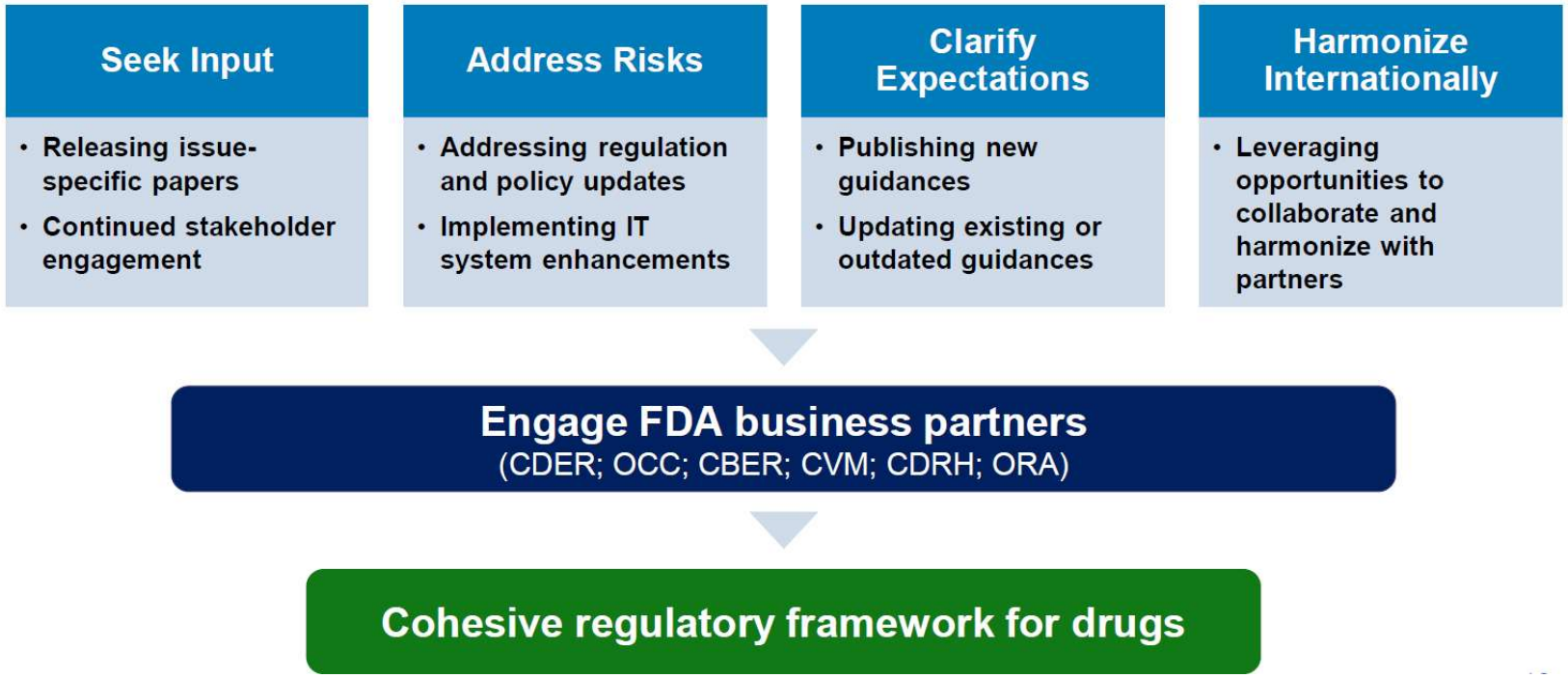
Agenda

1. Background and Regulatory Context
2. GSK Case Study and Ongoing Dialogue with Regulators
3. On the Horizon

Key Developments: FDA Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)



FDA's FRAME provided important 2023 concept paper for AI/ML in drug manufacturing and sponsored a critical dialogue through PQRI Workshop.

FDA recently included process models and CPV as part of a draft ICH advanced manufacturing concept paper.

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-framework-regulatory-advanced-manufacturing-evaluation-frame-initiative

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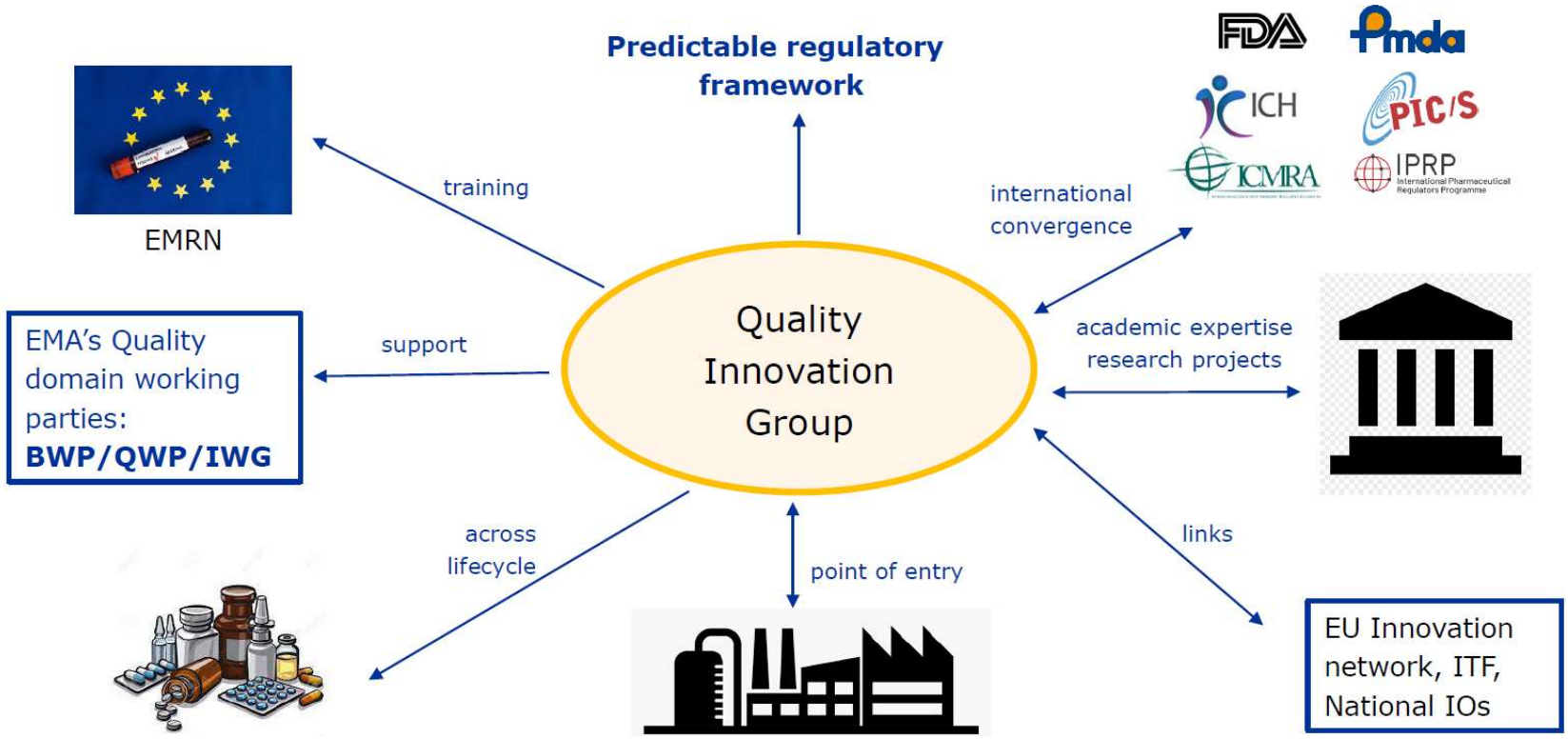
Key Developments: EMA Quality Innovation Group (QIG)

Several EMA QIG Digital Listen and Learn Focus Group (LLFG) Meetings have provided a critical forum for discussion of process modeling and AI/ML.

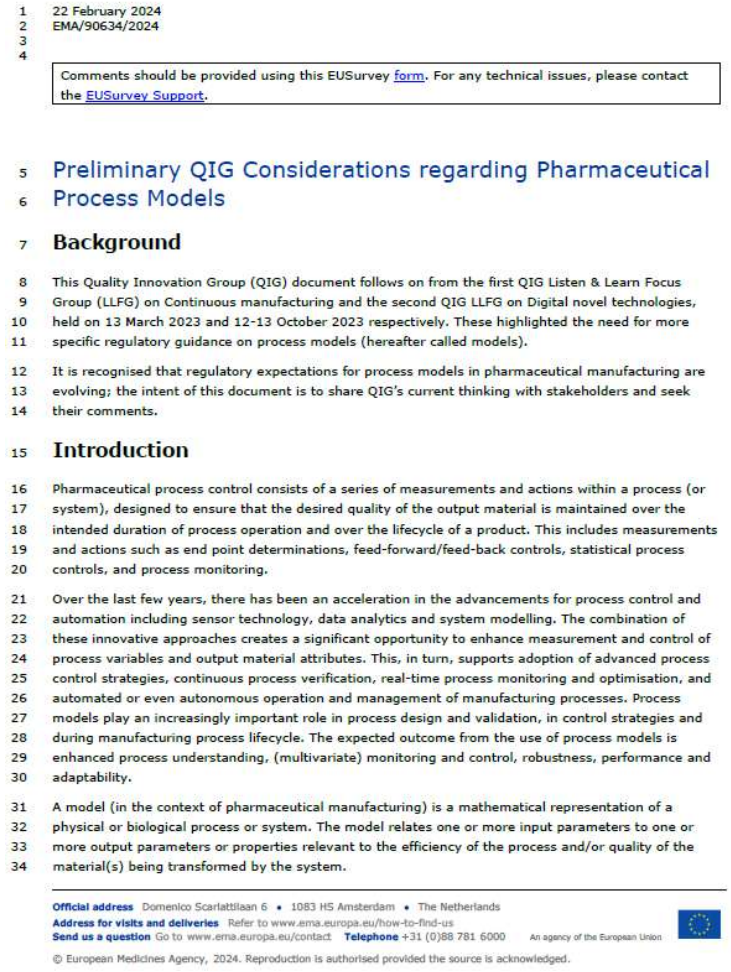
A forthcoming session will futher address case studies to inform updated guidelines.



https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/quality-innovation-group

https://www.ema.europa.eu/en/documents/report/report-listen-and-learn-focus-group-meeting-quality-innovation-group_en.pdf

EMA Considerations White Paper on Process Models



22 February 2024
EMA/90634/2024

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Preliminary QIG Considerations regarding Pharmaceutical Process Models

Background

This Quality Innovation Group (QIG) document follows on from the first QIG Listen & Learn Focus Group (LLFG) on Continuous manufacturing and the second QIG LLFG on Digital novel technologies, held on 13 March 2023 and 12-13 October 2023 respectively. These highlighted the need for more specific regulatory guidance on process models (hereafter called models).

It is recognised that regulatory expectations for process models in pharmaceutical manufacturing are evolving; the intent of this document is to share QIG's current thinking with stakeholders and seek their comments.

Introduction

Pharmaceutical process control consists of a series of measurements and actions within a process (or system), designed to ensure that the desired quality of the output material is maintained over the intended duration of process operation and over the lifecycle of a product. This includes measurements and actions such as end point determinations, feed-forward/feed-back controls, statistical process controls, and process monitoring.

Over the last few years, there has been an acceleration in the advancements for process control and automation including sensor technology, data analytics and system modelling. The combination of these innovative approaches creates a significant opportunity to enhance measurement and control of process variables and output material attributes. This, in turn, supports adoption of advanced process control strategies, continuous process verification, real-time process monitoring and optimisation, and automated or even autonomous operation and management of manufacturing processes. Process models play an increasingly important role in process design and validation, in control strategies and during manufacturing process lifecycle. The expected outcome from the use of process models is enhanced process understanding, (multivariate) monitoring and control, robustness, performance and adaptability.

A model (in the context of pharmaceutical manufacturing) is a mathematical representation of a physical or biological process or system. The model relates one or more input parameters to one or more output parameters or properties relevant to the efficiency of the process and/or quality of the material(s) being transformed by the system.

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- **Clarity on some very important issues:**
  - ***Shift to model risk terminology***
  - Model risk vs. role in control strategy
  - Emphasis on dossier content based on model performance
  - Limited registration of algorithms
  - Clarification of dossier content and validation requirements based on model impact

- **Thoughts:**
  - Assessment of model risk in isolation?
  - For low impact models, dossier content only necessary if model-based conclusions are filed?
  - Clarity that all models would not need to strictly meet GMP
  - Interesting section on "dual purpose" models predicting QAs as part of process design – need to think through this!
  - ***Model lifecycle and maintenance protocol – important to clarify scope here as some models may not be maintained!***

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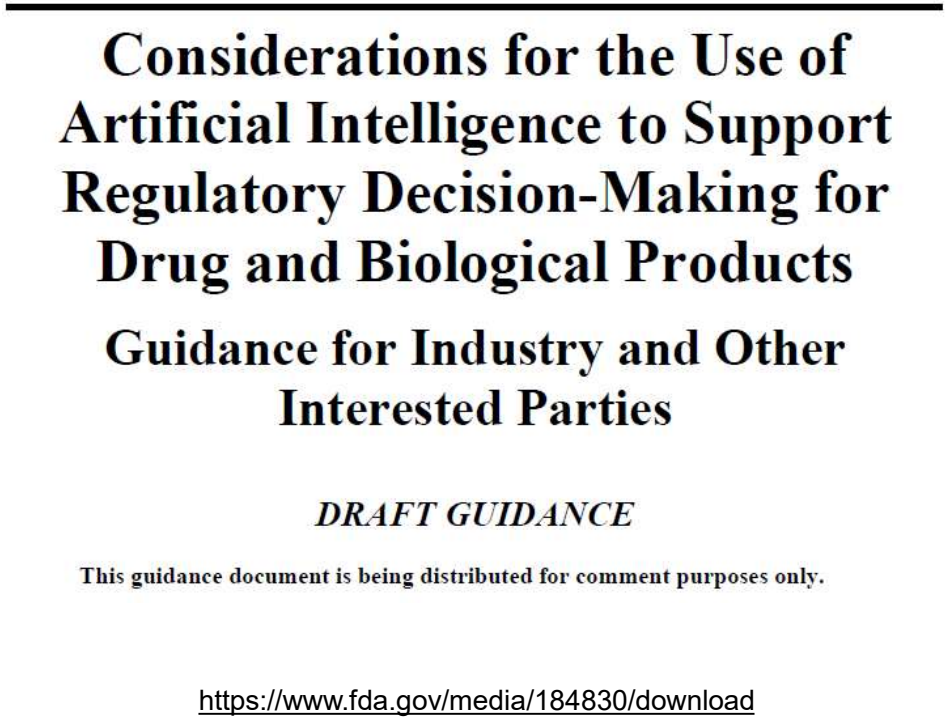
FDA AI Guideline



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

Guidance for Industry and Other Interested Parties

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

https://www.fda.gov/media/184830/download

- **Initial Manufacturing Perspective:**
  - Guidance closely linked to ASME 40, which is supported by EMA and FDA and show the merging consensus on model-risk based approach to the deployment of AI.
  - Link to the control strategy and the QMS in mitigating risk is positive.
  - Potential to enable development and deployment of AI in GMP manufacturing.
    - Example, Line 552 states: ”In general, detailed plans for life cycle maintenance ((e.g. model performance metrics, risk-based frequency for monitoring…triggers for model retesting) **should be made available for review as a component of the manufacturing site’s pharmaceutical quality system**, with a summary included in the marketing application for any product or process-specific models, in accordance with regulatory requirements”

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FDA Guideline: First Steps Toward Establishing Model Credibility

- **Step 1: Define the question of interest that will be addressed by the model**
  - "…describe the specific question, decision, or concern being addressed by the AI model"
  - Example for automated vision system: "Do vials of Drug B meet established fill volume specifications?"

- **Step 2: Define the context of use (COU) for the model**
  - Describe in detail
    - What will be modeled and how model outputs will be used.
    - Whether other information will be used in conjunction with the model output to answer the question of interest (i.e., different evidentiary sources)

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FDA Guideline: FDA Leans Into Model Risk Terminology

- **Step 3: Assess the AI model risk**
  - **Model Risk:** possibility that the output may lead to an incorrect decision that could result in an adverse outcome, and not risk intrinsic to the model.
  - **Model Risk = Model Influence x Decision Consequence**
    - **Model Influence:** Contribution of the evidence derived from the AI model relative to other contributing evidence used to inform the question of interest.
    - **Decision Consequence:** Significance of an adverse outcome resulting from an incorrect decision concerning the question of interest.
  - Different evidentiary sources are relevant when determining model influence.
  - Decision consequence is **not** influenced by COU, but **can** factor severity, probability, and detectability (see footnote 23).

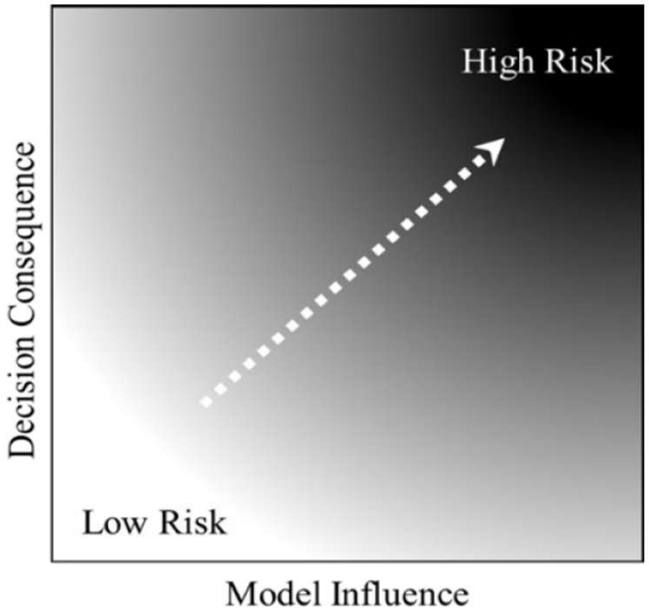

Figure 1. Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for decision consequence and model influence are independently determined.

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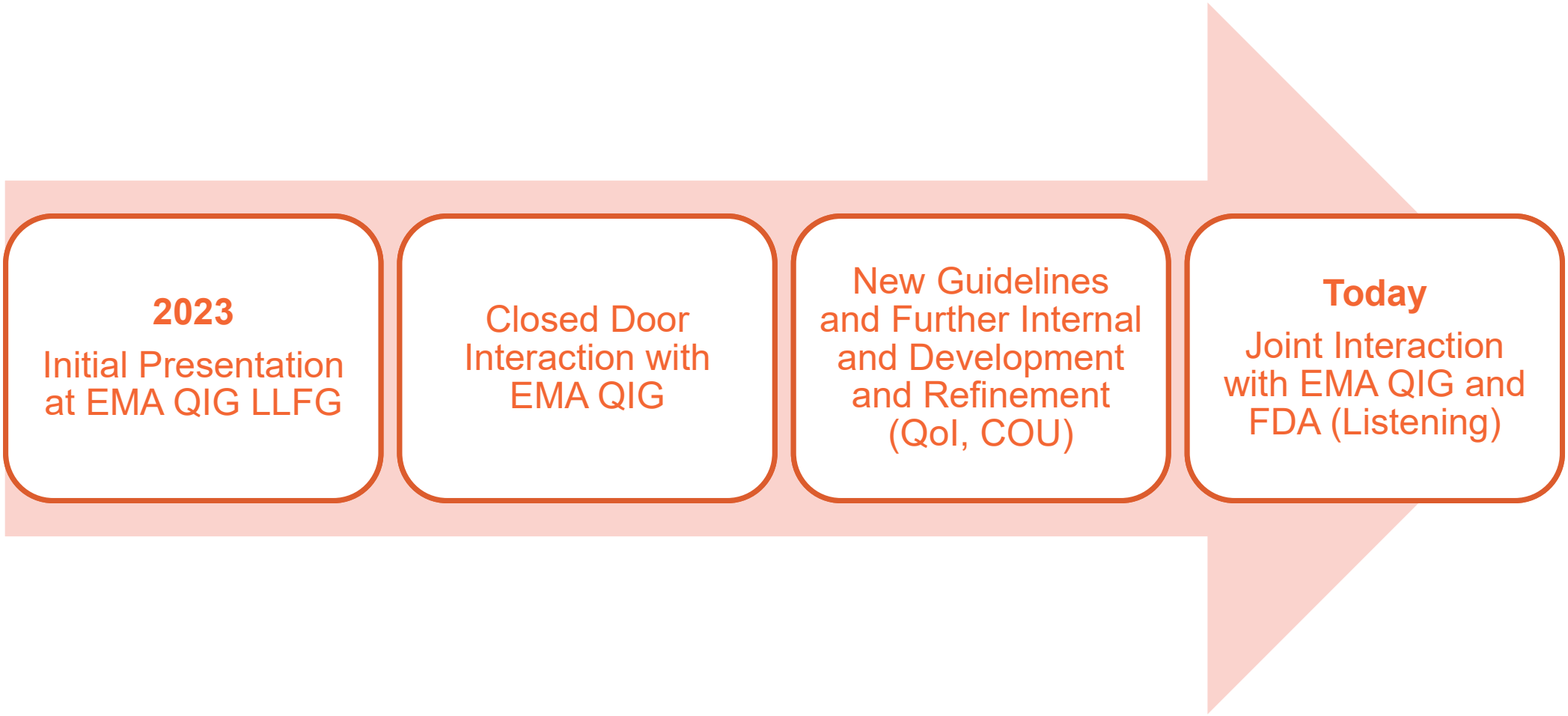
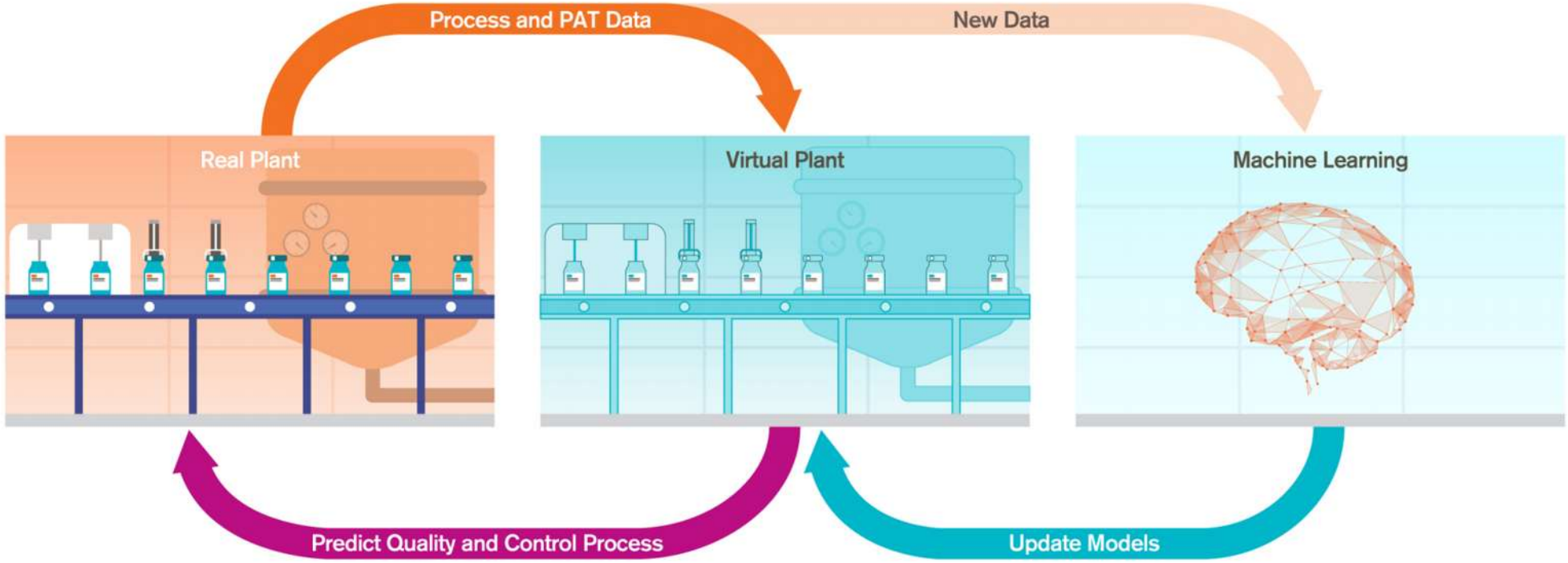
GSK Case Studies and Ongoing Dialogue with Regulators



Hybrid Process Models – Digital Twins



Online: Assurance of quality
Collect process data in real time, understand what is happening and provide optimal control

Offline: Accelerated development
Do in-silico development: simulate, test, optimize before experimenting in the lab

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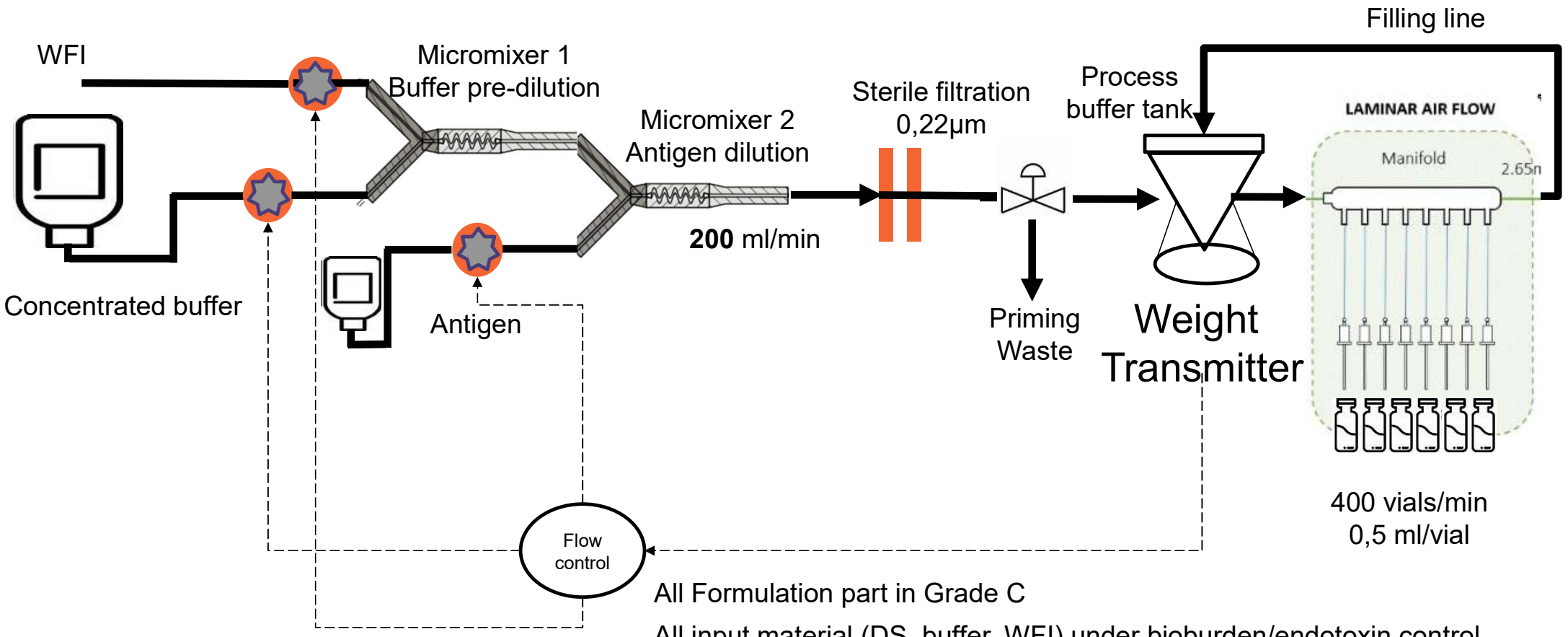
**Slide credit to Sandrine Dessoy, GSK*

GSK Case Study – Digital Twin for Continuous Formufilling



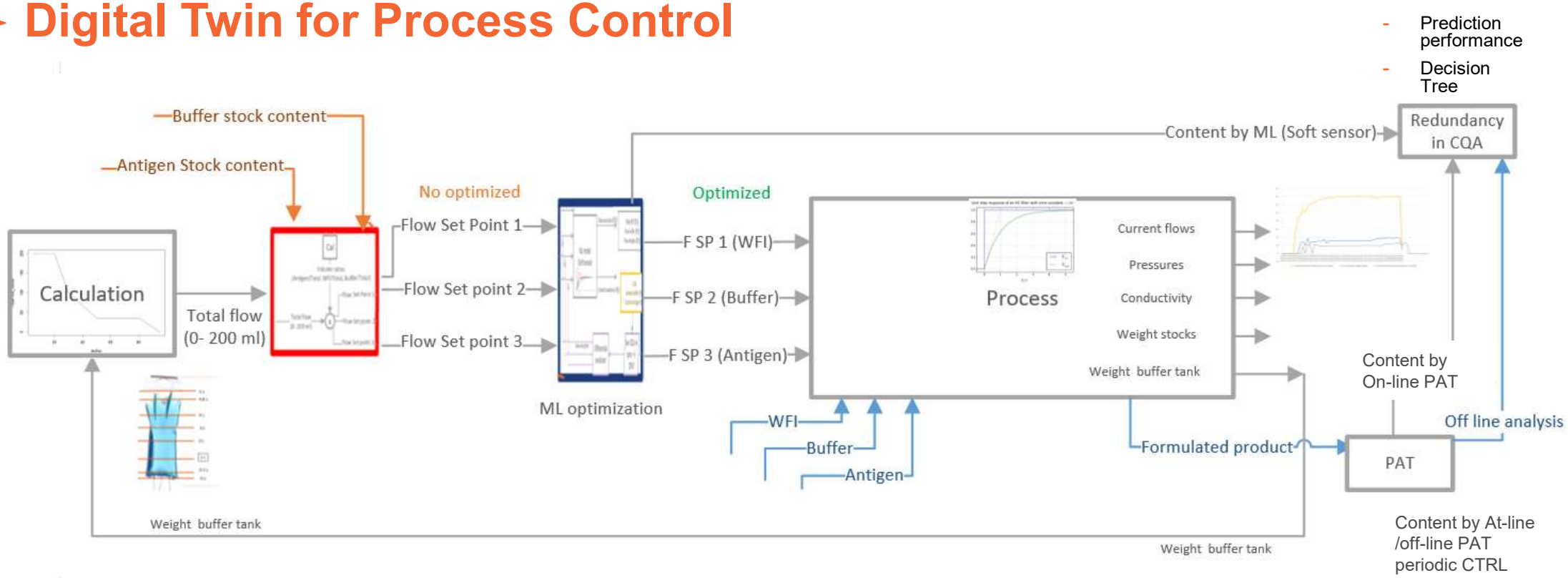
All Formulation part in Grade C

All input material (DS, buffer, WFI) under bioburden/endotoxin control

Single use assembly (bioburden control) including (POFF/PUPSIT)

Close system

Digital Twin for Process Control



- PAT Sensors (conductivity, flow, weight and pressure) and PAT probes (UV and NIR) provide data enabling real-time process monitoring based on Chemometrics models coupled with machine learning models (ML).
- Hybrid system model (“Digital Twin”) capable of simulating time profiles of product content and prediction of other attributes (conductivity, pH, concentration, etc.) from system inputs.
- Direct feedback loop to adjust process parameters to optimize product quality and minimize waste.
- **Full release testing is still carried out (i.e., NOT RTRT)**

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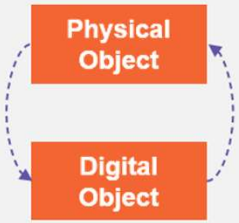
GSK Twin Level Definitions

Digital Twin Level 1

(Digital Model)

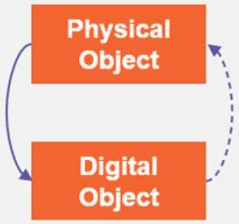


Development

- Reduce experimentation by in silico process development
- Training & process understanding

Digital Twin level 2

(Digital Shadow)

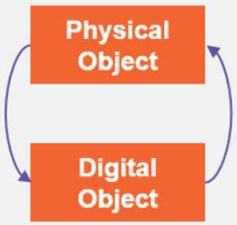


Introduction of new processes

- Provide advanced monitoring
- Recommend action if a trend towards deviation is detected
- CPPs are constrained

Digital Twin level 3

(Digital Twin)



New continuous process & batch processes after learning phase

- Provide advanced monitoring & advanced control to maintain CQAs at target

ICH Q8/Q9/Q10 Q&A PtC - Model Impact (Relevance Now?)

- **High-Impact Models:**
  - Prediction from the model is a **significant indicator of quality** of the product
  - Must have high precision and accuracy
  - Should be fully **validated** at commercial scale
  - Must be **maintained and updated** during the product lifecycle

- **Medium-Impact Models:**
  - Useful in **assuring quality** of the product
  - **Not the sole indicator** of product quality
  - Must have **appropriate precision, accuracy, and predictive power** to assess the probability of failure

- **Low-Impact Models:**
  - **Support** product and/or process development
  - Model predictions are **not the direct indicators for assurance of product quality**

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EMA QIG Feedback for GSK

Q: GSK is proposing that for a digital twin model for a continuous process which controls the process but where there is **no decrease in end product testing**, the model will need limited verification at the commercial scale and that model performance can be demonstrated as part of PPQ where superiority of model-based control can be demonstrated over classical (parametric) controls. Is this acceptable to the QIG?

A: The QIG asked GSK to clarify if the proposal is to provide in the application verification elements instead of validation elements. GSK confirmed the understanding of the proposal, indicating small-scale experiments are planned to test the model. For example, by introducing intentional disturbances experiments/simulations to demonstrate that the digital twin could identify, anticipate problems, and adapt accordingly the process. **The QIG agreed that given that the end product testing remains fully in place, the model would be considered low/moderate impact and in level 2, hence this approach should be acceptable.** GSK asked whether this proposal would be acceptable for a level 3-type model as well. **The QIG indicated that if standard QC release is done with no RTRT, this approach can be still acceptable (e.g., the model remains medium impact), provided model performance is appropriately demonstrated by designed small scale or in silico experiments.** The QIG also acknowledged that the digital twin model performance will improve over time as further data is collected. GSK confirmed that model performance will be verified and demonstrated, but not part of formal commercial-scale validation.

Model Verification Proposal and Path to Commercialization

Strategy for initial market supply

- Process boundaries defined based on the model and then experimentally verified
- Control strategy unchanged (CQAs tested as part of batch release)
- Model active during manufacture to control the process within the design space
- Adaptive model performance demonstrated as part of process 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**

Increased model risk

Future State

- Further model data provided in the dossier
- 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

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What About Adaptive Control More Generally?

Per ICH Q12:

- **Established conditions (ECs)** are legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.

- A **parameter-based approach** is one in which product development prior to regulatory submission provides a limited understanding of the relationship between inputs and resulting quality attributes and will include a large number of inputs along with outputs.

- A **performance-based approach** is one where ECs are primarily focused on outputs rather than inputs. This is enabled by knowledge gained from an enhanced approach, a data-rich environment, and an enhanced control strategy (e.g., **models**, PAT).

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EMA QIG Feedback for GSK

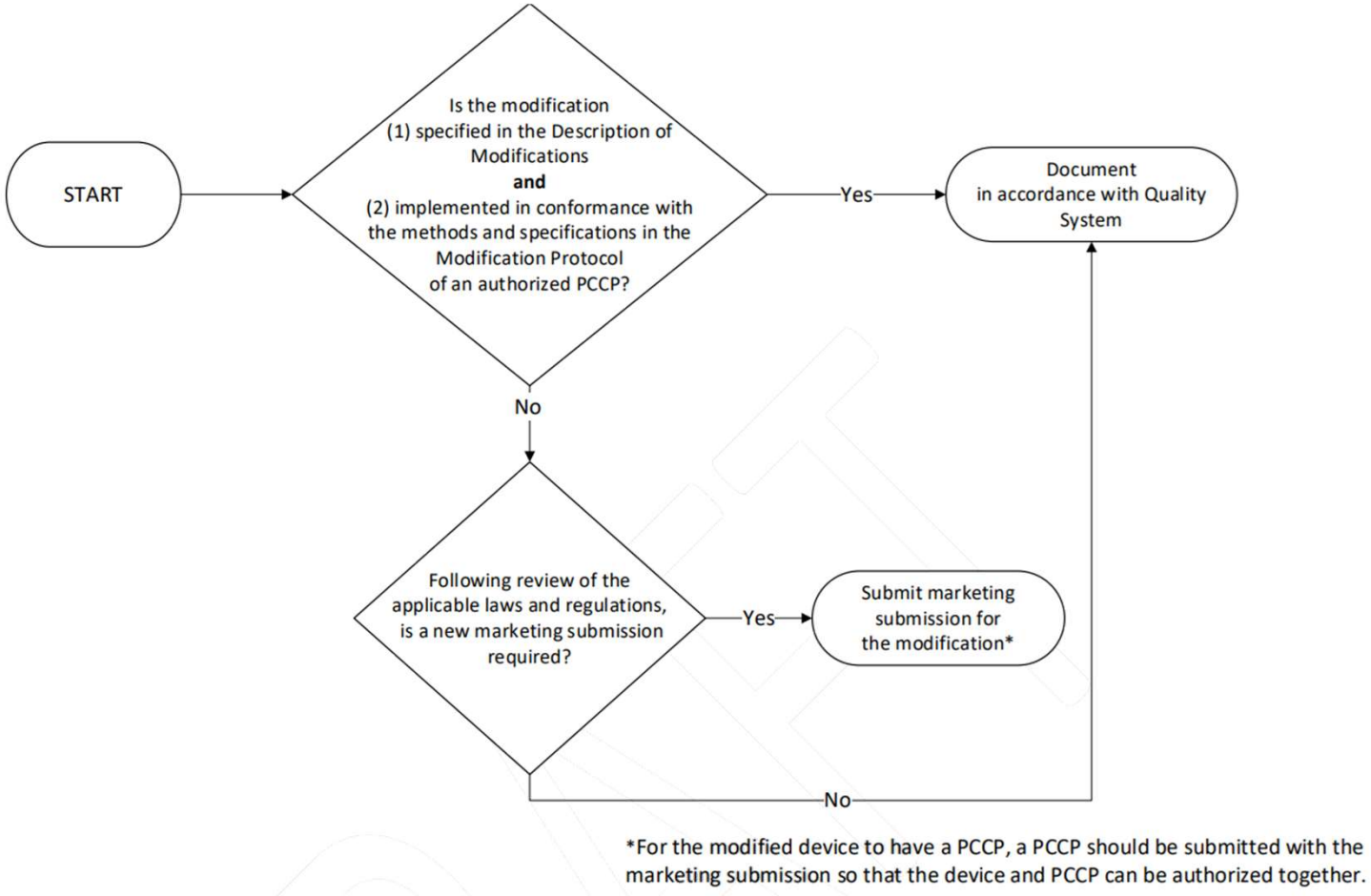
Q: Practical use of a digital twin for process control will mean that the process parameter setpoints adjust automatically, based on the model, within defined ranges. Conceptually, GSK believes this is justifiable based on the overall control strategy, including real-time verification of process outputs, and can be justified in the dossier. However, GSK are concerned that current guidance and requirements regarding "design space" (or moreover EMA expectations for parameter ranges/PARs) do not fully anticipate the envisioned scenario. Narrow interpretation and strict application of these design space guidelines could inhibit implementation and use of these models. **Can the framework described in ICHQ12 Section 3.2.3.1 for a "performance based" process control strategy be applied, such that the manufacturing process is not described by process parameter ranges?**

A: **QIG indicated that performance-based process control strategy per Q12 (i.e., one not described by fixed parameter ranges, but relies on the controls of the model) is recognized.** The QIG indicated that, unlike mechanistic or metabolic models, truly data driven models may not be fully understood. The QIG noted that EMA has reviewed dossiers presenting continuous manufacturing application (e.g., measure of humidity of the granules and on that basis the system adapting the process to ensure that at the end of the process the material was of acceptable quality). QIG noted this is less complex than the GSK digital twin but agreed that the same principles of performance-based controls can apply.

Tools for Model Lifecycle Management Are Now Available

- **FDA PCCP Guideline and Q12 PACMPs** gave us the tools, in theory, to reduce the need for registration of unnecessary model information, focusing instead on model-based ECs

- This tool is now explicitly called out in EMA QIG concept paper and **will be critical for performance-based ECs for high-risk models**.



https://www.fda.gov/media/166704/download

Engineering Parameter ECs and CFD Modeling

P.3.3. Critical Process Parameters for Dilution/Mixing of Bulk Drug Substance/Product

From → **To**

Process Parameter	Limit/Range
Reactor volume/fill	Scale and equipment dependent
Blend time	
Impeller speed	

Process Parameter	Limit/Range
P/V	Scale and equipment independent
Shear rate	

Millipore PowerMix 200

Scale UP

Mobius Mix 50/100

Pall Lev Mix 100

Sartorius Palletank 100

Scale ACROSS

Millipore PowerMix 100

Future of Change Management and Verification Using CFD Models

FROM

- **Equipment parameters are ECs**
- **Changes to scale and equipment parameters made under PQS require regulatory action**
- **Changing ECs requires prior approval**

TO

- **Engineering parameters are ECs**
- **Changes to scale and equipment parameters made under PQS require no regulatory action**
- **Approaches to change control include:**

OPTION 1

Changes made regularly with change control **defined case-by-case** → Assessor needs confidence in model. Requires detailed CFD model discussion and justification in the dossier; CFD **model in S2.2**?

OPTION 2

Changes are made following **pre-defined verification protocol** (approved during assessment) → More limited CFD description as **supporting information in S2.6**

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What's Next: Legislation and Regulation

OCTOBER 30, 2023

FACT SHEET: President Biden Issues Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence

BRIEFING ROOM › STATEMENTS AND RELEASES

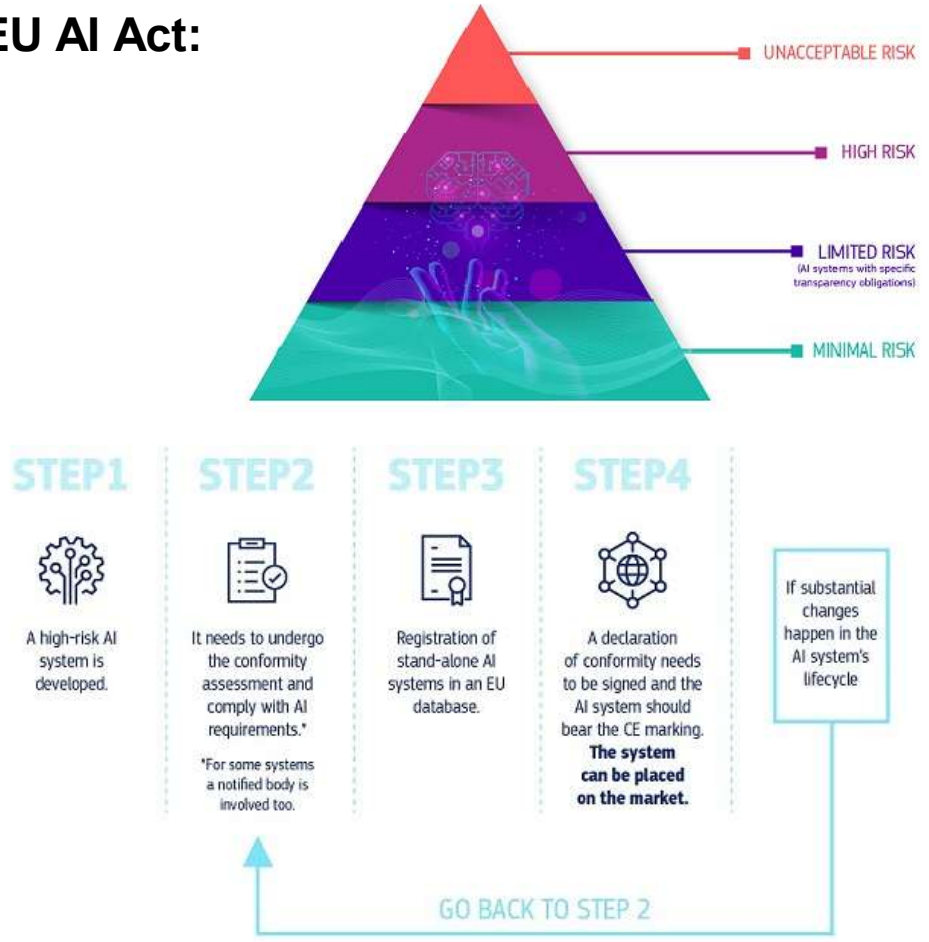
- **"The Executive Order establishes new standards for AI safety and security, protects Americans' privacy, advances equity and civil rights, stands up for consumers and workers, promotes innovation and competition, advances American leadership around the world, and more."**

https://www.whitehouse.gov/briefing-room/statements-releases/2023/10/30/fact-sheet-president-biden-issues-executive-order-on-safe-secure-and-trustworthy-artificial-intelligence/

- **"At least 12 (states) have enacted laws that delegate research obligations to government or government-organized entities to increase institutional knowledge of AI and better understand its possible consequences."**

https://www.brennancenter.org/our-work/research-reports/states-take-lead-regulating-artificial-intelligence

- **EU AI Act:**



https://www.consilium.europa.eu/en/press/press-releases/2023/12/09/artificial-intelligence-act-council-and-parliament-strike-a-deal-on-the-first-worldwide-rules-for-ai/

What's Next: Legislation and Regulation

OCTOBER 30, 2023

FACT SHEET: President Biden Issues Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence

REVOKED

- "The Executive Order establishes new standards for AI safety and security, protects Americans' privacy, advances equity and civil rights, stands up for consumers and workers, promotes innovation and competition, advances American leadership around the world, and more."

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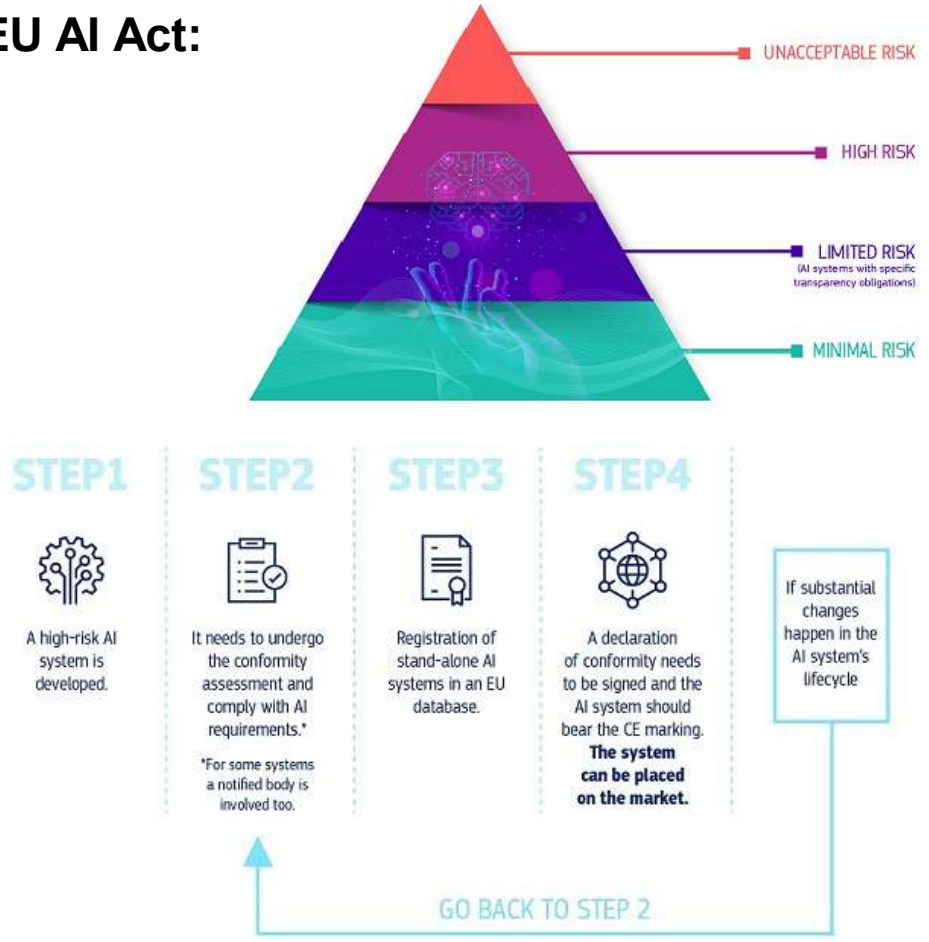


https://www.consilium.europa.eu/en/press/press-releases/2023/12/09/artificial-intelligence-act-council-and-parliament-strike-a-deal-on-the-first-worldwide-rules-for-ai/

What's Next: FDA 21 CFR 211.110 Guideline – Impact on Soft Sensors?

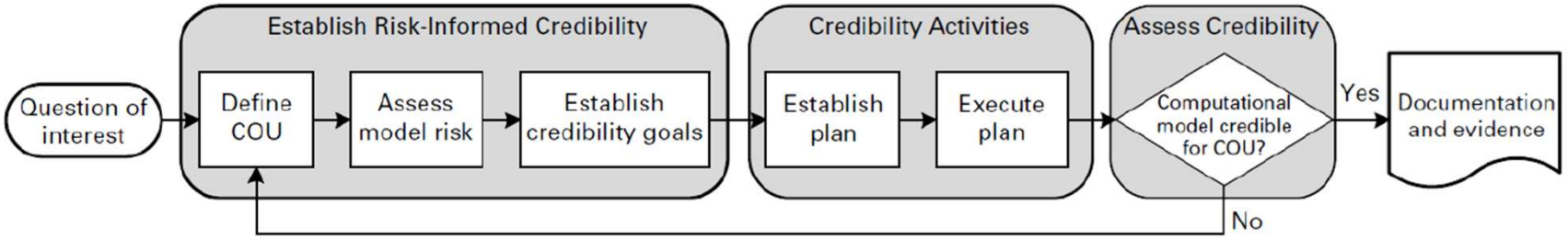
- **Thoughts on this?**

> FDA is aware of industry's interest in using in-process control strategies that rely solely on process models to satisfy the requirements of § 211.110. This includes interest in strategies that use process models in continuous manufacturing to predict in-process material uniformity and homogeneity without any testing or examination of the in-process material (whether direct or indirect). However, to date, FDA has not been made aware of process models that demonstrate that: (1) the underlying assumptions of the process model will remain valid during routine manufacturing; and (2) the manufacturer can detect if an underlying assumption is no longer valid (e.g., a continuous mixing model that assumes uniform mixing would be unable to detect that uniform mixing is no longer occurring due to material agglomeration on the walls of the mixer). In other words, current process models cannot ensure the continued validity of all of the model's underlying assumptions at all times, particularly during certain unplanned disturbances. In the event of an unplanned disturbance that is not accounted for by the model's underlying assumptions, such control strategies would be unable to prevent nonconforming in-process materials (e.g., nonhomogeneous powder blend) from continuing through production and being used "in manufacturing or processing operations for which they are unsuitable."[27,28] Therefore, control strategies that rely solely on current process models would be insufficient to satisfy the requirements of § 211.110.

https://www.fda.gov/media/184825/download

What's Next: Evoluation of ASME V&V 40

- **Model credibility** refers to the trust in the predictive capability of the computational model for the COU.
  - **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.
  - **Model risk** - possibility that the model may lead to a false/incorrect conclusion about device performance, resulting in adverse outcomes.



*Formally, ASME V&V 40 and CDRH guideline **do not apply to data-based models**.*

***ASME VVUQ 70 sub-committee** is developing standard for AI/ML model credibility*

***ASME VVUQ 80 sub-committee** is developing standard for pharmaceutical process*

Expanding Regulatory Science Academic Modeling Initiatives

What is the Digital CMC CERSI?

The Digital CMC CERSI is a centre of excellence to accelerate the adoption of digital technologies in regulatory processes to ensure faster, more efficient delivery of medicines to patients with reduced environmental impact.

Working collaboratively with a consortium of partners, it will drive the integration of technologies such as AI, machine learning, and hybrid models into regulatory frameworks for Chemistry, Manufacturing, and Control (CMC).

It is one of seven projects funded by **Innovate UK**, in partnership with the **Medicines and Healthcare products Regulatory Agency (MHRA)**, **Office for Life Sciences** and the **Medical Research Council (MRC)**. The Digital CMC CERSI tackles a range of regulatory challenges experienced across the medicines manufacturing industry including:

- **Many regulatory guidance documents for digital models**
- **Complexity of AI and data-driven predictive systems**
- **Quality, integrity and security of data**
- **Regulatory expertise shortage**
- **Academic, industry and regulatory translation gap**
- **Public perception**

https://cmac.ac.uk/digital-cmc-cersi

Inno4Vac is a public-private partnership that addresses scientific bottlenecks in vaccine development.
It proposes to develop predictive biological and mathematical models of vaccine performance and bio-manufacturing.
Artificial intelligence combined with big data and computational modelling will be used to build an open-access and cloud-based platform for in silico vaccine efficacy assessment and development. Controlled human infection models and cell-based human in vitro 3D models will be developed to enable early evaluation of vaccine efficacy and prediction of immune protection.
Finally, for vaccine bio-manufacturing the goal is to establish an open source in silico simulation platform for guiding the production of vaccine candidates and associated stability testing.

https://www.inno4vac.eu/

What's Next: Other Emerging Points of Focus

- **GMPs and Annex 22**
- **2025 ICH process modeling topic proposal**
- **ISO/IEC TC 62 ahG 11 (standardization of the credibility assessment of computational modeling and simulation)**

- **PMDA/AMED**

Innovative Pharmaceutical Manufacturing Technologies and AI & Machine Learning

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has developed a guideline on continuous manufacturing (ICH Q13 Guideline), which was officially notified in Japan in 2023. As this guideline also mentions the utilization of models, it is easy to anticipate that AI and machine learning will increasingly be applied to pharmaceutical manufacturing and quality control in the future. In this presentation, I will introduce PMDA's efforts and expectations regarding continuous manufacturing and the application of AI and machine learning from a regulatory science perspective.

Mr. Yoshihiro MATSUDA
Pharmaceuticals and Medical Devices Agency
Principal Senior Scientist for Quality

https://www.informa-japan.com/cphifcj/seminar/en/index.php?currentYear=2025&

ISPE AI CoP and RQHC Pharmaceutical Modeling Team

InTouch | November / December 2024

ISPE Announces ISPE AI®

ISPE recently announced ISPE AI®, an initiative aimed at aiding the pharmaceutical industry in realizing the potential of artificial intelligence (AI). The initiative will include a multifaceted approach to supporting the industry in AI readiness, beginning with the launch of the ISPE Community of Practice (CoP) on AI.

Over time, ISPE will also provide new ISPE Guidance Documents, additional conference sessions, new training courses, and more resources that focus on AI-related planning and implementation.

https://ispe.org/pharmaceutical-engineering/november-december-2024/ispe-announces-ispe-air

- **RQHC Pharmaceutical Modeling Team**
  - Feedback to EMA QIG Process Modeling Considerations Paper.

https://ispe.org/sites/default/files/regulatory/2024/Comments%20from%20ISPE%20to%20EMA%20QIG%20for%20Process%20Models%20Postion%20FINAL.pdf

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