Challenges and Opportunities for AI-ML - A Regulatory Perspective

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Disclaimer

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

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Agenda

- GSK use cases
- Regulatory backdrop
- Industry challenges
- Opportunities

Background – Model Classification

Data-Driven/Empirical	Hybrid (Semi-Empirical)	Knowledge-Driven/Mechanistic
Feature: • Based on **data-driven observations** and used to model the relationship between the system input and output variables. • Can be useful for **complex systems** and typically **requires minimal understanding** of the science governing the system. • These models should not be extrapolated beyond the ranges covered by the input data. **Example:** • Multivariate models • Regression models • Neural networks	**Feature:** • **Combine empirical and mechanistic** to describe a well-understood part of a system to build a mechanistic model, and where there is a gap or less clearly understood aspect of a system, empirical models can be developed. • Predictive within the experimental ranges where its empirical part was calibrated but has the advantage of still providing a physical interpretation due to its mechanistic part. **Example:** • Scale-up models using fundamental relations of a system, combined with data-driven experimental data.	**Feature:** • Based on understanding the science governing the system and used to **model the underlying phenomenon** of a system and its relationship to the output. • Can perform **predictions beyond the ranges covered (extrapolation) by the input data** (depending on the validity of the underlying assumptions). **Example:** • Chemical Kinetics Models • Population balance model (PBM) • Computational Fluid Dynamics (CFD)

Deep Learning for Automated Visual Inspection

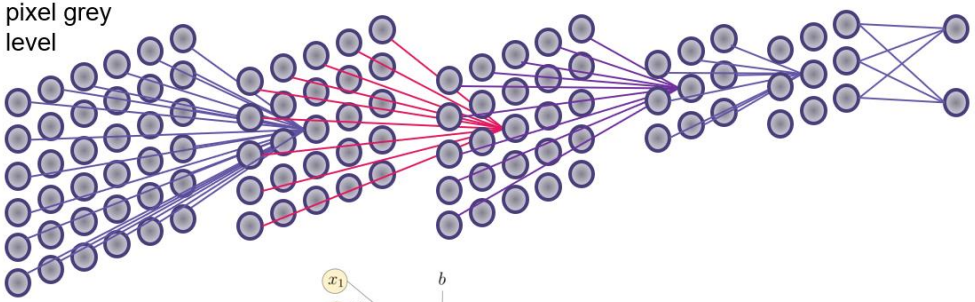
Conform images

Crack images

First layer to input each pixel grey level

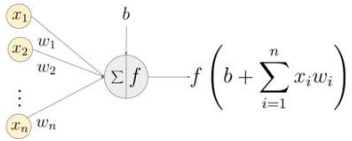
Early layers to detect big features

Last layers for final defect classification



Conform class

Crack class

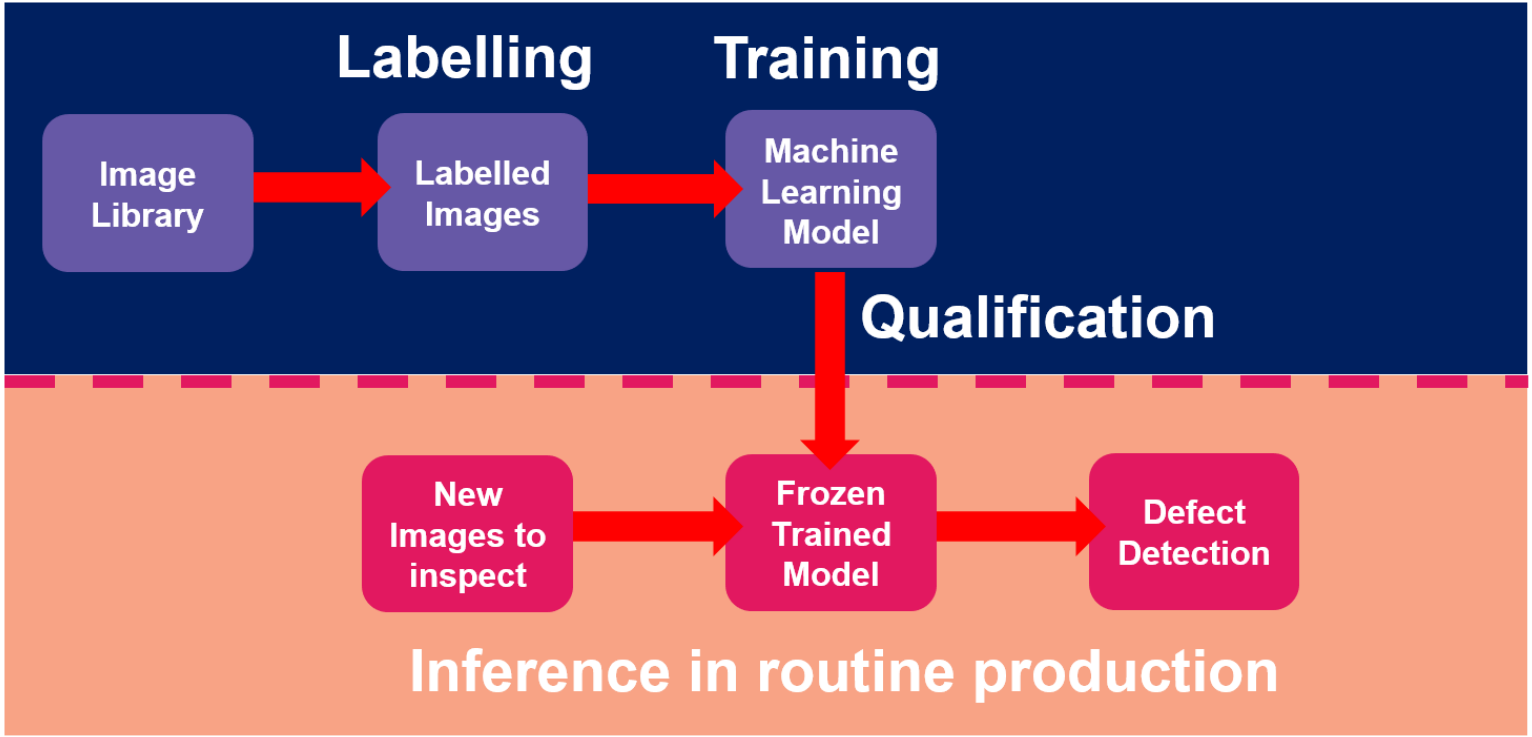


Each neuron is a weighted sum of others with bias

Many Layers designed to optimize image classification, containing from 3 to 50 million parameters to adjust

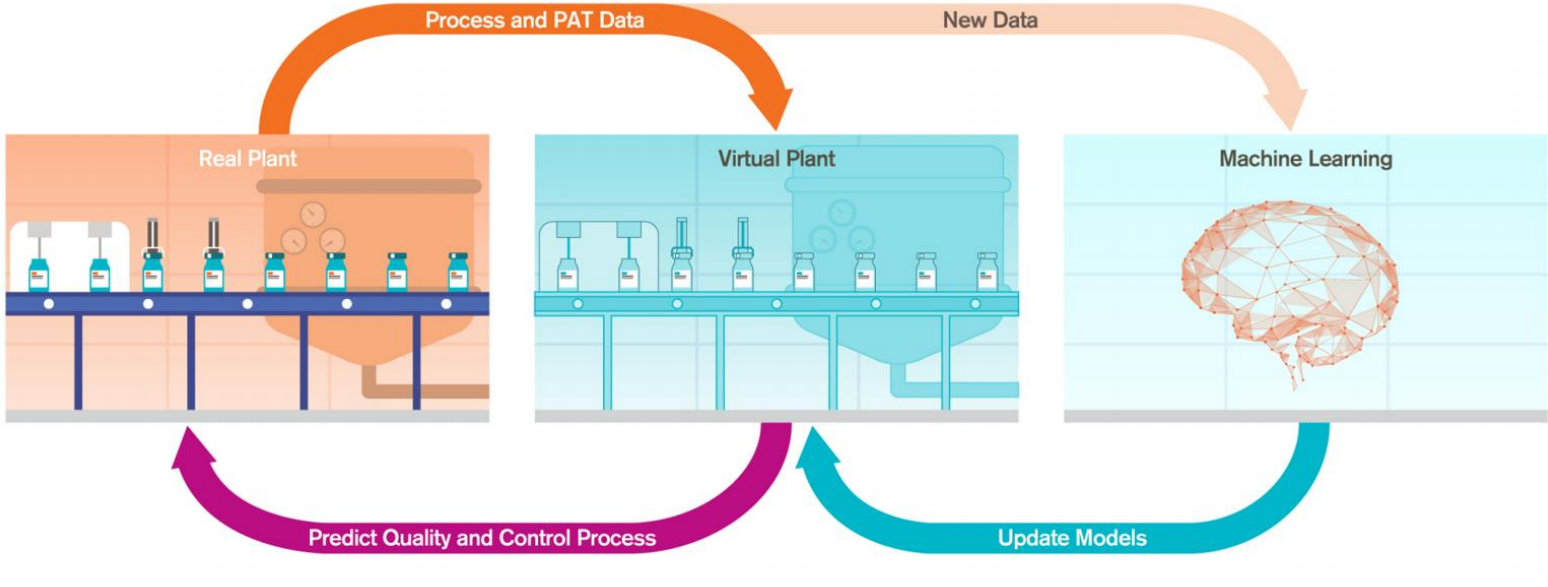
*Slide credit to Romain Veillon, GSK

Deep Learning for Automated Visual Inspection



*Slide credit to Romain Veillon, GSK

Hybrid Process Models – Digital Twins

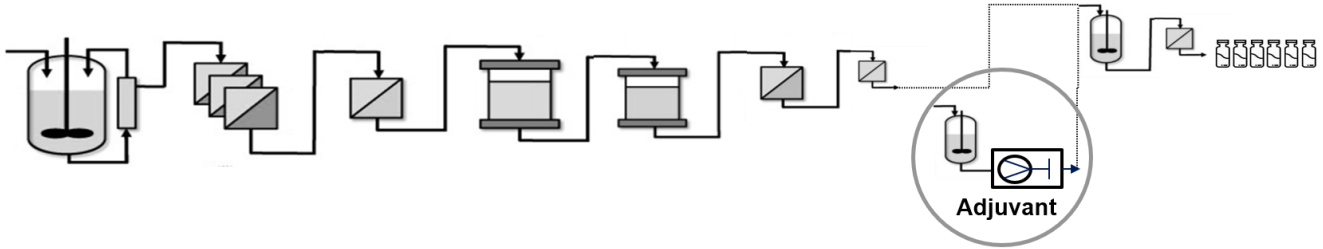


Online: Assurance of quality
Collect process data in real time, understand what is happening and provide optimal control

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

**Slide credit to Sandrine Dessoy, GSK*

Digital Twin for Vaccine Adjuvant Manufacture



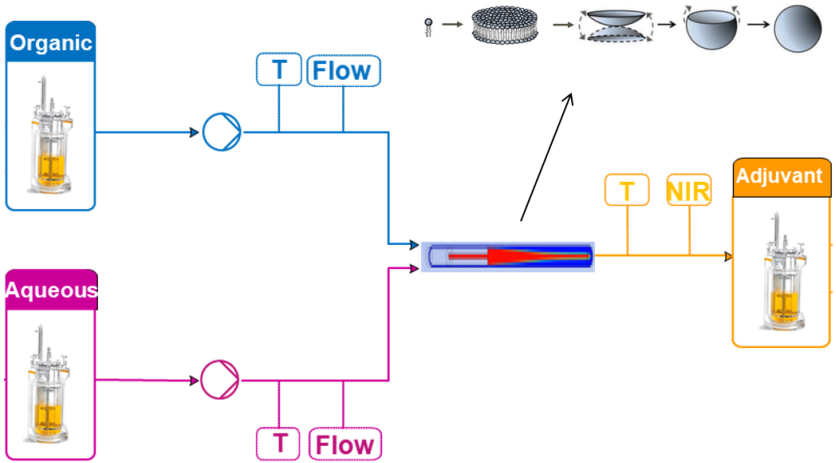
Critical Process Parameters

- Flow rates
- Concentrations
- Temperature

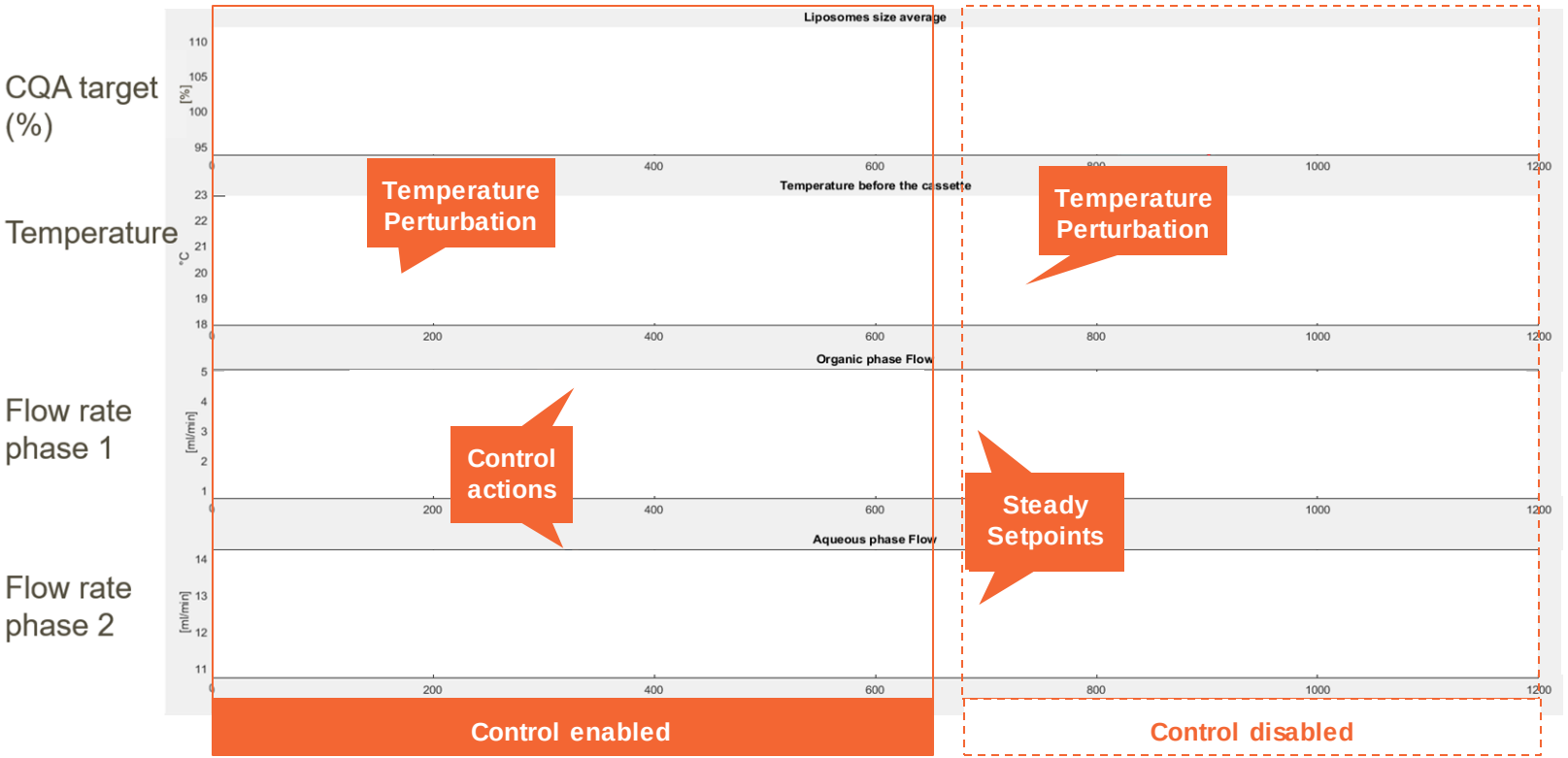
MODELS to PREDICT & ACT

Quality Attributes

- Adjuvant concentration
- Adjuvant size distribution



*Slide credit to Sandrine Dessoy, GSK



*Slide credit to Sandrine Dessoy, GSK

Regulatory Backdrop

**Slide credit to Gert Thurau, Roche*

Regulatory Backdrop

- *AI/ML Action Plan & Upcoming Guidance*
- **Model Change Management**

- *Biophorum Manufacturing Models WP*
- **Process Model Lifecycle Management**

- *EFPIA AI Position*
- **Proposals for EU Legislative Framework**

- *FDA Simulation in Medical Device Submissions*
- **Model Credibility**

- *ISPE AI Maturity Model for GxP*
- **Model Validation**

- *EFPIA Position - Digitalization in Pharma Manufacturing*
- **Challenges and Opportunities**

Regulatory Backdrop

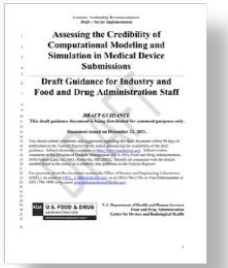
DEVICES


Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

U.S. FOOD & DRUG ADMINISTRATION

Sep 2016


Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

U.S. FOOD & DRUG ADMINISTRATION

Dec 2021

Jan 2021

Knowledge-Based Models ⟷ **Data-Based Models**

DRUGS


ICH

5.3 Model Validation and Model Verification During the Lifecycle

Model validation is an essential part of model development and implementation. Once a model is developed and implemented, verification continues throughout the lifecycle of the product.

Dec 2011

product quality attributes. There are limited industry standards and FDA guidance available for the development and validation of models that impact product quality, which can create challenges in establishing the credibility of a model for a specific use.

May 2023

*Slide credit to Marc Horner, Ansys

Challenges for AI/ML Models

- Registration and LCM (dossier vs PQS, change classification)
- Lack of clear definitions and ambiguity in some existing definitions
- Training and calibration
- Acceptable use of platform data sets
- Requirements for validation/verification according to model impact level (per ICH Q8/9/10 Q&A PtC)
- Requirements based on explainability (i.e., “need to have” vs “nice to have”)
- Extent of need for a “human in the loop,” esp. for low/medium impact
- GMP aspects, including data management and governance

Challenges – Example of Definition Ambiguity

Definition of Artificial Intelligence	
FDA - Artificial Intelligence in Drug Manufacturing (link)	**EMA - Reflection Paper on the Use of Artificial Intelligence (AI) in the Medicinal Product Lifecycle (link)**
"A branch of computer science, statistics, and engineering that uses algorithms or models that exhibit behaviors such as learning, making decisions, and making predictions."	"Artificial intelligence, refers to systems that display intelligent behaviour by analysing their environment and **taking actions – *with some degree of autonomy*** – to achieve specific goals."

EMA definition implies a pre-requisite for the model to take specific actions without human intervention. Very important distinction from FDA definition.

Challenges – "Human in the loop"

- EMA AI Reflection Paper: *"**For all models, especially those where there is no human-in-the-loop**, a risk management plan should be developed that defines likely risks of fail modes of the algorithm, e.g. what are the consequences of incorrect predictions/classifications as well as monitoring and mitigation/correction approaches, such as how to trigger a suspension/decommission of the model and how to suspend or decommission it."*

- Implication – according to this proposal, **by default**, an AI/ML model is higher risk than a human (e.g., do we establish a RMP for visual inspection?).
  - Is this really true, esp. for a GMP process with a well formulated, comprehensive control strategy in a GMP environment subject to PQS and routine inspections?

Consider alternative for CMC – **RMP required for any medium or high impact model (as defined in ICH Q8/9/10 Q&A Points to Consider) that takes autonomous action with no human-in-the-loop.**

Opportunity – Performance-Based Approaches

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).

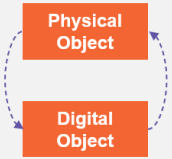
GSK Discussion with EMA QIG

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.

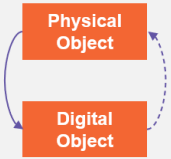
Opportunity – Digital Twin Model Impact

Digital Twin Level 1
(Digital Model)



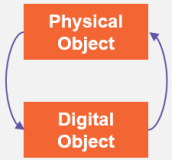
Development
- Reduce experimentation by in silico process development
- Training & process understanding

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

GSK Discussion with EMA QIG

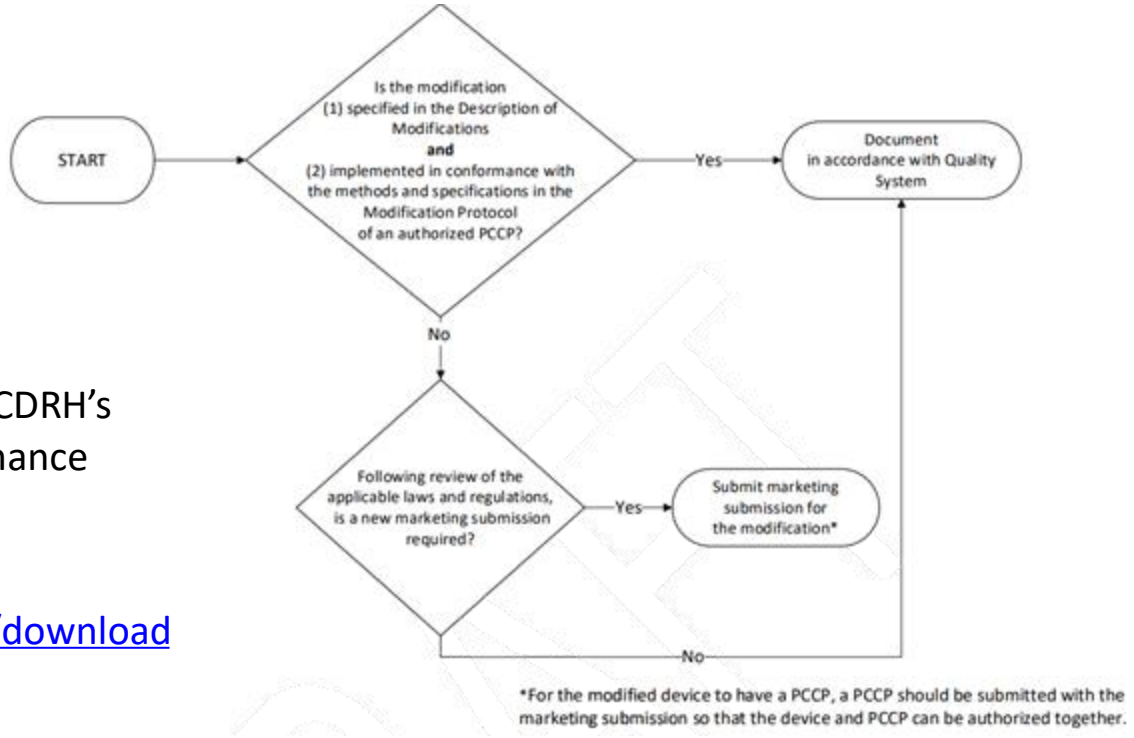
Q: GSK is proposing that for a digital twin model for a continuous process which controls the process but where there is no decrease in end product testing, the model will need limited verification at the commercial scale and that model performance can be demonstrated as part of PPQ where superiority 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.

Opportunity – PACMPs

- PACMPs can essentially do what CDRH's PCCP does by integrating performance based criteria.

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



Opportunity – AMT & Platform Tech Designation

Advanced Manufacturing Designation

- Applicant must "*use an established technique or technology in a novel way, that will substantially improve the manufacturing process for a drug while maintaining equivalent, or providing superior, drug quality*"
- Agency can "expedite the development and review of an application" or supplement and leverage data.

Platform Technology Designation

- Utilized by and facilitates manufacture or development of more than one drug/biologic sharing common structural elements through a standardized production or manufacturing process(es).
- Agency "…may expedite the development and review of any subsequent application…" including additional meetings, leveraging inspectional findings and platform data (cross product).

Opportunity – ASME VVUQ 70

COMMITTEE CENTRAL › VVUQ 70 VERIFICATION, VALIDATION, AND UNCERTAINTY QUANTIFICATION OF ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

ASME VVUQ 70 Charter

- **Coordinate, promote, and foster the development of standards that provide procedures for assessing and quantifying the credibility of artificial intelligence and machine learning algorithms applied to mechanistic and process modeling.**
- **Charter approved in November 2019**
- **No standards published to date**

VVUQ Standards Committee in Computational Modeling and Simulation

- **VVUQ 10** – VVUQ in Computational Solid Mechanics
- **VVUQ 20** – VVUQ in Computational Fluid Dynamics and Heat Transfer
- **VVUQ 30** – VVUQ in Computational Simulation of Nuclear System Thermal Fluids Behavior
- **VVUQ 40** – VVUQ in Computational Modeling of Medical Devices
- **VVUQ 50** – VVUQ of Computational Modeling for Advanced Manufacturing
- **VVUQ 60** – VVUQ of Computational Modeling for Energy Systems
- **VVUQ 70** – VVUQ of Machine Learning
- **VVUQ 80** – VVUQ in Computational Modeling of Pharmaceutical Products

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Thank you

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