EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Quality Innovation Group (QIG)

3rd Listen and Learn Focus Group (LLFG) meeting report

4 – 5 June 2024

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Introduction

Following the two Quality Innovation Group (QIG) Listen and Learn Focus Group (LLFG) meetings held in 2023 and additional meetings with individual applicants, where stakeholders highlighted the need for further guidance on pharmaceutical process models, the QIG developed its preliminary considerations regarding pharmaceutical process models and published them for public consultation.

QIG invited stakeholders to provide their written comments on this document and to identify areas for clarification, discussion and/or improvement. Stakeholders were also invited to put forward case studies for the 3rd LLFG showing the applicability of the considerations included in the document, its benefits and/or limitations, and discuss lifecycle management aspects.

The scope of this 3rd LLFG meeting was to discuss the most relevant comments received during the public consultation and the applicability of the QIG preliminary considerations to the case studies presented by stakeholders, to exchange views, clarify any potential misunderstanding, identify challenges and get additional information to progress this topic further.

The event was attended by approximately 120 participants from industry, academia and regulatory authorities, including representatives from US FDA, PMDA and Swissmedic.

The meeting comprised the following sessions:

Tuesday, 4th June 2024

1. Introduction to QIG, meeting scope and objectives of the 3rd LLFG meeting
2. QIG Preliminary Considerations on process models
3. Session 1
    - 3.1. Presentation on the Application of the EMA Preliminary Considerations to Real Process Model Examples, EFPIA
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Wednesday, 5th June 2024

4. Session 2
    - 4.1. Presentation on *In Silico* Modeling, Amgen
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    - 4.3. Presentation on Machine Learning Process Model for Prediction of Variant Attributes in a Monoclonal Antibody DS Process, F. Hoffmann-La Roche

4.4. Presentation on Cross-Program mRNA Process Models with Interpretable Machine Learning (ML), Moderna

4.5. Plenary discussion

4.6. General sum up on challenges, solutions and follow-up

5. Next steps and closure of the meeting

The next sections of this report summarise the discussions and key points raised by industry and academia stakeholders during each of the sessions. While it is emphasised that these are the views expressed by stakeholders, the QIG took note of these, and they will be considered in the revision of the QIG preliminary considerations document.

1. Introduction to QIG, meeting scope and objectives of LLFG

The Quality Innovation Group (QIG) is a multi-disciplinary group comprising GMP inspection and quality assessment expertise, both for chemical and biological medicinal products, established in 2022 to deliver on key goals of the EMA's Regulatory Science Strategy to 2025 (e.g. enabling and leveraging research and innovation in regulatory science and catalysing the integration of innovative science and technology into medicines development).

The QIG is the point of entry for developers to discuss innovative CMC approaches under scope. Its goal is to ensure EU has a predictive regulatory framework to enable implementation of innovative technologies which will ultimately benefit patients in the EU. QIG also collaborates with other regional regulatory agencies to enable widespread implementation of these technologies via established multi-regional organisations.

The QIG priority topics in 2024 are process models and platform technologies. As indicated above, the objective of this LLFG was to discuss with stakeholders key points raised during the public consultation on the QIG preliminary considerations documents and its applicability to case studies, to identify challenges and areas that require further reflection.

2. QIG Preliminary Considerations on process models

In early 2024 QIG published its preliminary considerations on process models to communicate its current thinking on the use of performance-based approaches in pharmaceutical manufacturing and support the development, implementation and lifecycle management of process models in pharmaceutical manufacturing. It brings forward a risk-based classification of models to determine the level of validation and documentation required.

The key comments received during the public consultation pertained to: the scope of the document (e.g. whether machine learning (ML) and Artificial Intelligence (AI) were in the scope), terminology (need to align among different sources), dossier versus PQS expectations, model validation, model performance and model lifecycle considerations. Comments centred on considerations of the medium-risk models category and respective expectations. It was emphasized that the document is not intended to increase regulatory burden for medium-risk models, but to clarify expectations and thus provide predictability in the development and implementation of models.

The QIG will take into consideration the discussions that took place during this 3rd LLFG meeting as well as the comments received during the public consultation on the document and any information from any follow up 1:1 meeting with stakeholders to further revise the QIG preliminary considerations document.

3. Session 1

3.1. Presentation on the Application of the EMA Preliminary Considerations to Real Process Model Examples, EFPIA

EFPIA stressed the importance of the QIG document and QIG initiatives to enable use of process models in development and in the control strategy. In terms of global harmonization efforts and regulatory expectations, EFPIA cited links between guidance related to models from the ICH, EMA, and elsewhere. EFPIA noted overlap and divergence in terminology of these guidances.

The presentation emphasized the importance of risk categorization, focused on the model's role in the control strategy, in enabling the adoption of models and highlighted that the need to ensure regulatory guidance enables model implementation. EFPIA highlighted overlap between the ICH term of model "impact" and the ICHQ9 and ASME V&V 40 concepts of "risk".

The presentation used two process models in manufacturing as exemplars: a simple hybrid design space model for blister strip sealing and a more complex digital twin model for continuous formulation and filling of a vaccine.

The former model, based on fundamental physics and engineering principles, defines operational boundaries for sealing, while the latter simulates the entire vaccine manufacturing process. Both models, despite their complexity, can be classified as low risk, depending on their role in the control strategy. EFPIA highlighted the QIG consideration for process models is an evolution of long-established discussions related to control strategy in ICHQ8-11 and noted overlap and learnings with considerations for design space.

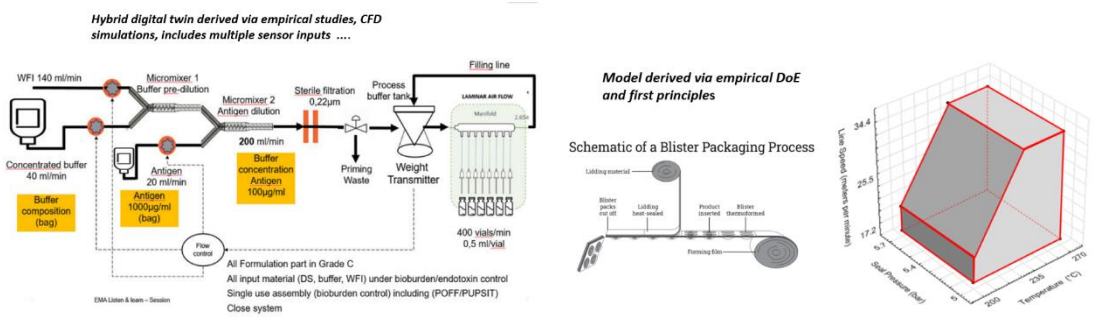

Figure 1. Schematic of a digital twin model for continuous formulation and filling of a vaccine and of a hybrid design space model for blister strip sealing.

Complex and simple process models can both be low risk

EFPIA considered that because the QIG document mainly concerns registration considerations, a focus on subsequent lifecycle management of the dossier content was relevant. Therefore EFPIA also highlighted the opportunity to learn from previous related guidances to limit requirements for PQS-like documents, (e.g. change protocols), as content in the dossier as these would be a burden on lifecycle management and should be assessed during inspections. Overall EFPIA noted the primacy of considering the model's role in the overall control strategy in determining risk and how this must link to limiting the amount of registered regulatory detail in the dossier in order to not disincentivize the use of more advanced process control technologies.

From the perspective of EFPIA, the integration of AI and ML in pharmaceutical manufacturing is an evolution of the ongoing modelling discussion. EFPIA views Good Manufacturing Practice (GMP) as a

low-risk framework for implementing AI and ML, and emphasizes the existing role of human involvement and explainability in AI systems within the Pharmaceutical Quality System (PQS).

In summary, EFPIA underscored the need to enable and incentivize all uses of process modelling in pharmaceutical manufacturing, and the need for a harmonized and flexible regulatory framework.

3.2. Uncertainty Quantification of Process Models: Key to Risk-Informed Decision Making throughout the Product Life Cycle, ISPE

Process models are used to make decisions on the process design and execution throughout the entire product lifecycle such as defining the best set-point conditions for the process, setting control ranges or controlling the process in real-time. Each decision comes along with the question: "What is the risk the model-based decision poses to product quality and derived patient safety and efficacy?"

Uncertainty quantification (UQ) is a generic method applicable to all types of models to estimate this risk. UQ can yield a quantitative estimate, e.g. a certain model-based decision leads to a 20% likelihood of being outside certain acceptance criteria. Depending on the context of use and the situation where the model is applied (low to high-risk situations) different levels of risk might be acceptable depending on the role of the model in the control strategy. In a high-risk case, the risk of a 20% likelihood of being outside acceptance criteria is unlikely to be acceptable. However, in a low-risk case it might be acceptable. UQ empowers us to react and mitigate the risk. In contrast, the mean prediction is a point estimate and does not hold information about the uncertainty, and the residual risk of meeting acceptable product quality based on use of the model alone is unknown.

To enable systematic uncertainty quantification, the presentation introduced five types of errors and uncertainty.

1. Errors in (physical) model specification: e.g. a linear instead of non-linear model has been chosen.
2. The error model could be mis-specified, e.g. a normally distributed error is assumed instead of a non-normally distributed error.
3. Uncertainty in the parameters of the model, called epistemic uncertainty.
4. Uncertainty in estimate of the random noise of the output, called aleatory uncertainty.
5. Uncertainty in the model inputs, e.g. measurement error in process parameters.

Although assumptions on (1) and (2) can and should be checked after model training by appropriate tools, use of these tools was not in scope of the presentation.

Considering only epistemic uncertainty (3) leads to confidence intervals around the prediction, which are usually insufficient for most use cases as they only depict uncertainty around the predicated mean and do not take random variation, e.g. batch-to-batch variation or analytical method variation, into account. Specifically for biopharmaceutical processes those variations can be significant. Combining types (3) and (4) leads to tolerance intervals around the prediction. Those depict the uncertainty around the (future) population of runs. This is very useful when making decisions on the (future) population of runs, e.g. when setting control ranges[1].

If all sources of uncertainty are considered, including input data uncertainty (5), this leads to total uncertainty of the prediction. This can be compared to external acceptance criteria to estimate the

[1] G. J. Hahn and W. Q. Meeker, Statistical intervals: a guide for practitioners. in Wiley series in probability and mathematical statistics. New York: Wiley, 1991.

total residual risk to product quality. If the residual risk is acceptable a model can be regarded valid for a certain context of use. Hence, UQ is a useful tool in validation of process models.

3.3. Case-study on the Qualification of Mechanistic Downstream Process Models as Part of Regulatory Submissions, Boehringer Ingelheim

A case-study was presented to demonstrate the applicability of the preliminary QIG considerations regarding pharmaceutical process models and provide feedback for future guidance documents.

The case-study showcased the application of a mechanistic model to support the development and regulatory filing of a chromatography polishing step of a therapeutic protein. The model's context of use included the identification of critical process parameters (CPPs) and critical material attributes (CMAs) as well as the definition of proven acceptable ranges (PARs) as part of the process control strategy. In this context, model predictions replaced experimental process characterization studies as current evidentiary standard to inform both questions of interest.

Boehringer Ingelheim presented the qualification of the model and the data used during a regulatory filing following the preliminary considerations. In general, the preliminary QIG considerations were found applicable and a valuable step towards overcoming current regulatory challenges in applying process models. The following key points and feedback were provided:

Feedback to Q1: Model risk assessment

Considering the presented model context of use, the model risk was classified as medium since model-based evidence constitutes the key source of evidence, but model simulations are not active element of the process control strategy, and the product quality is always ensured by additional product monitoring such as final batch release testing. The model classification was found in alignment with the illustrative examples provided in the preliminary considerations. While preliminary considerations regarding model risk analysis were supported in general, it was commented that the current lack of more systematic guidance on how to determine model risk may lead to inconsistencies in the assessment and interpretation of model risk among different applicants. To enhance clarity and consistency in the classification of the model risk, an adaptation of the risk assessment described in the ASME V&V 40-2018[2] was proposed.

Feedback to Q2: Model description

Boehringer Ingelheim supported the preliminary considerations that, in the case of a medium risk model, the model description should include a description and justification of the model structure and the data used for model development. The presentation emphasized the importance of prior knowledge in the case of mechanistic (knowledge driven) models to justify the choice of model assumptions and select experiments for model development.

Feedback to Q3: Model validation

It was suggested to differentiate more clearly between statistical and mechanistic models regarding the expected validation effort. With reference to the ICH Points to Consider Document, it was emphasized that in the case of some mechanistic models, validation evidence may also be provided in the form of prior knowledge (e.g. validation evidence from previous projects). With reference to the ASME V&V 40-2018 and FDA guidelines, it was further explained that in the case of mechanistic

[2] ASME V&V 40-2018. Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices

models, model validity can also be supported by "supportive evidence". Supportive evidence includes, for instance, the plausibility of determined model parameters and the goodness-of-fit of complex process behavior achieved during model development.

3.4. Sensor-fusion case-study, Hovione

Hovione presented a case-study of a hybrid process model based on Sensor Fusion approach to determine the endpoint of a drying unit operation. The case-study uses 1) a chemometric model based on Near Infrared (NIR) hard sensor to predict solvent content via direct measurement of the powder bed; 2) a drying mechanistic model soft sensor that takes real-time process parameters as inputs to predict solvent content; 3) an adaptative method to dynamically adjust model parameters against NIR data, and; 4) sensor fusion using Kalman Filter combining both predictions into one with lower uncertainty.

This model was classified as medium risk, as per *EMA Preliminary QIG Considerations regarding Pharmaceutical Process Models*. The model would be used as part of a process control strategy with other related measurements (monitoring of process parameters vs. acceptable range and release testing). The model can be prospectively reclassified as high risk if used to surrogate solvent content release testing.

Considerations on model validation and lifecycle management were presented, examining three main components of the model: NIR model, mechanistic model, and the adaptative element (sensor fusion). NIR models are well established through existing guidelines (e.g. ICH, EMA, USP, EP) and standards (e.g.: ASTM), and therefore shortly addressed.

Mechanistic models' validation was mentioned to require adequate frameworks: 1) since a simple comparison of quantities of interest obtained from simulations and experiments without the quantification of all the uncertainties involved is prone to misleading conclusions, and; 2) to enable the extrapolative capacity inherent to these models. In the case presented, the ASME VVUQ40 framework, based on demonstrating model credibility, was proposed. It provides a model validation approach that is science and risk based, including verification of code correctness and numerical accuracy, and quantification of uncertainties. This can be achieved by making use of historical data (not necessarily from the process in scope), by running planned simulations, and/or by executing experimental protocols (if needed to cover enough variability).

The validation of the adaptative element can also follow VVUQ40 framework but requires further considerations. The credibility assessment should include a clear rationale of the need for parameter optimization. Additionally, since each sensor fusion prediction has a dynamically calculated uncertainty, it was proposed to establish an upper bound that determines acceptable uncertainty. This threshold determined based on the validation data from process and/or simulated experiments, would be imbedded in the model use.

Lifecycle management principles and requirements were deemed similar for all components. Standard Operating Procedures (SOPs) should be in place for lifecycle management activities as part of the Pharmaceutical Quality System (PQS) and based on monitoring pre-defined evaluation criteria.

Hovione welcomes guidelines that reflect regulatory requirements and expectations on process models considering the possible approaches (including those containing adaptative elements). Hovione also considers it key that guidelines are harmonized across regulatory regions (e.g. ICH) and with an adequate balance between what is to be managed by PQS and what needs regulatory interaction. Additionally, there should exist mechanisms allowing Industry to present and discuss with Regulators specific cases, even if not associated with a specific submission.

3.5. Predictive Models for accelerated process design and development of high-quality medicines, Pfizer

Pfizer presented on the transformative potential of predictive models in accelerating the process design and development of high-quality medicines. The focus of this presentation was two-fold:

1. Demonstrate application of predictive models in process development activities through two case studies: a mechanistic bin blending model and a machine learning model for gravimetric powder feeders.
2. Emphasize the necessity for harmonized regulatory guidelines that promote the use of process models.

Predictive Models in Process Design and Development

Predictive models offer several key benefits in pharmaceutical development:

- Accelerated development times - Offering scale-up guidance, operating space de-risking, and resolving the speed-quality conundrum.
- Cost and time efficiency: Enable extensive analysis reducing the experimental effort, saving both time and costs associated with material usage.
- De-risking through exploratory analysis: Allow for the investigation of aggressive and edge points in processes at a low cost, providing a deep look into process performance and insights that are otherwise difficult to measure.
- Regulatory support: Provide digital data to support process development and regulatory filings.

Case Studies Overview:

A. Mechanistic Bin Blending Model:

Risk Level: Low to Medium.

This model uses the Discrete Element Method (DEM) to simulate the blending process of powders at different scales. It is particularly useful in oral dosage form manufacturing, where achieving a uniform blend of individual powder components is critical.

Benefits: Enhances understanding of industrial-scale blending, supports experimental trials, aids in pre-experimental process design, evaluates material behaviour under various operational conditions, and identifies potential process risks and solutions. This approach reduces the need for extensive experimental trials, which is especially beneficial for commercial-scale production of expensive products.

B. ML Model for Gravimetric Powder Feeder:

Risk Level: Low

This machine learning model predicts the performance of gravimetric feeders, which are essential for continuous processing. These feeders provide precise dosing of materials to ensure the correct blend composition in dosage forms.

Benefits: Addresses the poor flow properties of APIs, predicts feed factors, and de-risks process development. This approach leverages material property libraries and advanced algorithms to ensure accurate predictions, reducing the need for first-principles models that often fall short in this context.

The presentation concluded by addressing future challenges and directions for digital design in drug product development. The salient points included are:

- The need for standardizing platform technologies like Discrete Element Method (DEM) and Computational Fluid Dynamics (CFD).
- Establishing best practice guidelines like VVUQ standards and harmonizing regulatory guidelines for model application.
- Clarity on the regulatory expectation on model validation and lifecycle management
- Strong emphasis on external publications which will ensure that computational models are well-supported in regulatory submissions.
- Continuous interaction with regulators to align expectations and ensure the effective integration of digital and modelling data in drug development processes.

4. Session 2

4.1. In Silico Modeling, Amgen

This presentation focused on the integration and application of computational modeling in biopharmaceutical development and manufacturing, aligning closely with regulatory expectations and industry best practices.

The presentation outlined the clear and complete regulatory framework that encourages the use of in silico evidence in drug development. It highlighted the importance of the ASME Verification and Validation 40 Standard along with ICH Q8/Q9/Q10, which provides a non-prescriptive yet structured approach to model documentation, emphasizing risk-based approaches. The ASME VVUQ 40 Standard has become a crucial framework for modeling practitioners, ensuring robust model verification, validation, and applicability.

Amgen's In Silico Modeling Platform is detailed, showcasing its foundation on three pillars: assets (models and data), technologies, and processes. This approach facilitates continuous improvement and operational integration of computational models, which are essential for achieving a widespread adoption of virtual experimentation.

The presentation discussed the Mixing Analysis Toolkit, which has been in development and use since 2016. The primary aim is to foster decision agility and enhance operational efficiency through better mixing processes in various unit operations like media/buffer tanks, ultrafiltration/diafiltration tanks, and bioreactors, where mixing homogeneity is crucial. It uses fundamental conservation equations for momentum and species transport, applicable across different scales. The model asset is implemented using commercial and open-source software, allowing for extensive virtual experimentation and realistic visualization of mixing processes.

The sustainable use of the Mixing Analysis Toolkit requires advanced technologies like High-Performance Computing (HPC) and Application Modeling Frameworks. These technologies ensure the reproducibility and scalability of computational solutions. Open-source contributions, like the one available on GitHub (GUMPS), and web-based model deployment environments are also emphasized for democratizing access to in silico modelling.

Amgen has developed a Standard Operating Procedure (SOP) that codifies the necessary activities to establish model credibility. This SOP is adapted from the ASME VVUQ40 standard and is crucial for assessing the risks associated with the models, ensuring that they meet the required credibility for decision-making processes.

The presentation showcased specific instances where the Mixing Analysis Toolkit has been applied, such as in manufacturing deviations and technology transfers. These applications highlight the model's role in identifying and addressing issues related to mixing uniformity, which can significantly impact product quality (which is determined by analytical methods).

Dev Ops practices are crucial for the lifecycle management of modeling assets, as evidenced by Amgen's use of Git for version control, continuous integration/deployment practices, and GxP model lifecycle management tools. This approach ensures that modeling activities are maintained at high standards and can be seamlessly integrated into regulatory and quality management systems.

The presentation concluded with insights into the regulatory perspective provided by the EMA QIG document on process models. It emphasized the need for appropriate documentation and risk assessment for models used in regulatory submissions. Appropriate risk considerations can lead to summary model documentation in dossiers/CTD, while additional details can be made available for inspection in the PQS. The authors recommend limiting dossier information required for low risk models, and keeping required dossier information for medium- and high-risk models to concise summaries only, as PQS processes provide more flexibility and speed than presenting detailed information in dossiers/CTD, which is a trend that will become increasingly more relevant as breakthrough innovations continue to shorten drug development cycle times.

4.2. Lyophilization Modelling for Process Development and Control, GSK

GSK presented several considerations on the "Preliminary QIG considerations regarding pharmaceutical process models" issued from the QIG working group in February 2024 and the main implication on the digital twin for lyophilization process.

The digital twin consists of a data architecture for data collection, pretreatment and storage and a series of models implemented in an online server that performs all the specific tasks required to manage business risks during development and manufacturing, see **Error! Reference source not found.**.

The models under development can serve four main objectives:

- Process optimization;
- Process monitoring;
- Predictive process control;
- Real Time Release (RTR)

All these tasks could be accomplished with different modelling strategies and in general through a combination of deterministic and data-driven models.

GSK highlighted general agreement with respect to the EMA QIG preliminary considerations document. As specified in the document, the model risk (impact) is determined by the application of the model itself. The same model used for different goals may have a different level of risk (impact). As a consequence, data-driven models should not be considered differently from deterministic models, but the requirement in terms of model qualification and validation will depend on the intended use of the model.

With regard to this specific case-study, process development and optimization is mainly achieved using deterministic models; for this application, the model is considered "no impact" or "low impact" and would be managed under the PQS. Process monitoring, a typical data driven application, is intended for a process supervision and predictive maintenance at GMP scale. In this case GSK foresees a "low

impact" scoring. Predictive process control consists of the use of mathematical models and control logics for the operation of the equipment and the real time control of the equipment. In this case the mathematical model, either deterministic or hybrid, has a clearer potential impact on the product that is a "medium risk/impact" if subject to a standard batch release testing. The same model used to ensure product quality and quantify critical quality attributes (CQAs) without standard release testing would likely be categorized as a "high risk (impact)" model. Overall, the category of risk (impact) determines the requirements in terms of documentation to be submitted in the MAA dossier.

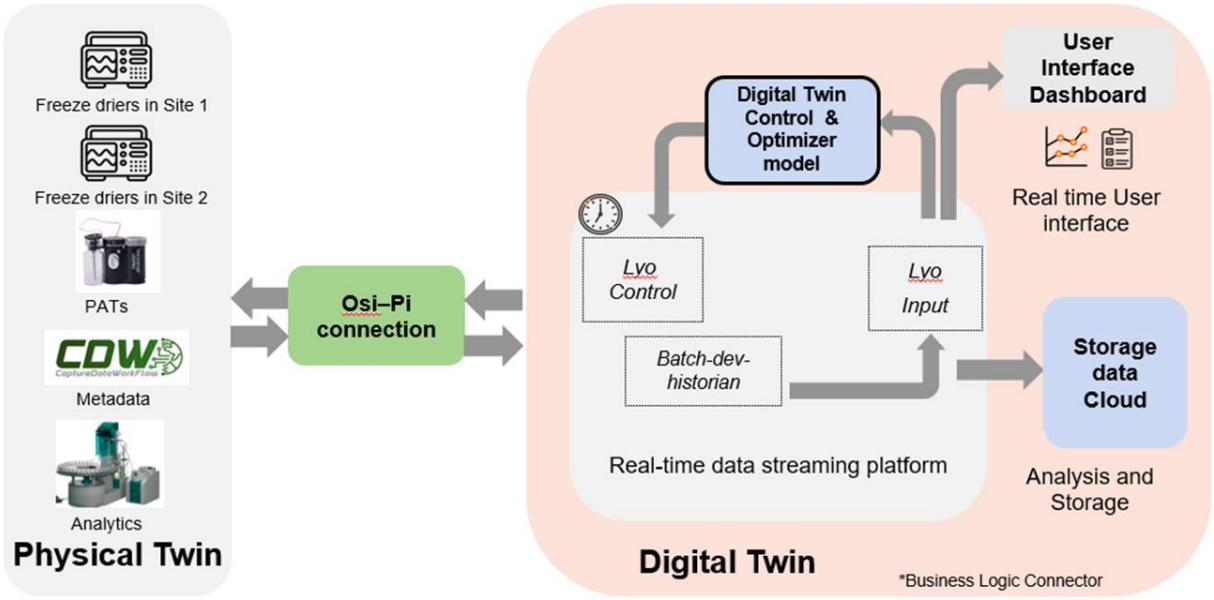

Figure 2. Data architecture and workflow of the digital twin for lyophilization.

The mathematical models will be embedded in the Product Development stream framework (i.e., used for process development and understanding in the early phase of process development, qualified and validated, as needed, while proceeding through the clinical development stages and ultimately transferred to a GMP lifecycle management process including regulatory updates, as appropriate).

Last but not least, the implementation of a digital twin in manufacturing, (i.e., a mathematical model is ultimately responsible for the operation of the equipment and to ensure the product quality) demands a shift from a recipe-based framework to a design space based one. GSK proposed the idea of validating and registering a region of safe conditions in which the equipment could operate to maximize the benefits instead of a specific recipe and a list of set lyo process set points.

4.3. Machine Learning Process Model for Prediction of Variant Attributes in a Monoclonal Antibody DS Process, F. Hoffmann-La Roche

This presentation showed the application of a ML-based model for the prediction of CQA-related variants in a monoclonal antibody drug substance process and classified it as a low risk-model.

The process model will be applied post-launch in a commercial process to optimize the cell culture titer, while ensuring that the levels of IEC acidic variants (initially defined as CQAs) stay within specification limits. The model is being developed leveraging a combination of static (offline sample values) and dynamic (real-time process parameters) data, across both process development (small scale) and commercial (at scale) manufacturing. The deployment of the model after completion of the

model development is planned in an "open-loop" mode, i.e. the results of the model and any processing decisions based on it will be overseen by a qualified supervisor.

The process model is qualified as low risk based on the considerations of its intended use, additional related measurements and the risk of failure and incorrect use of the model.

The model is used to drive a process decision within a registered and validated range of a critical process parameter. The initially registered and validated control system and ranges remain the same, i.e. same process parameter acceptable ranges, same CQA specification limits, same intermediate in-process control samples, etc. The values of the predicted CQA values are not used for quality release. The release decisions are made independently based on QC testing. The mode of operation is open loop with qualified human intervention and an automation system monitors and ensures that process parameters run within validated range. Therefore, the risk of failure and incorrect use is assessed as low with no impact on product quality or patient safety.

With respect to the EMA QIG Preliminary Considerations on Process Model document, the Roche feedback firstly referred to the classification system based on low-medium-high risk models, all of which are assumed to have to be registered. However, there are a wealth of process modelling applications for monitoring-only or additional characterization used which are currently not registered. To avoid increasing the burden on the application of this element of advanced manufacturing, it is suggested that an additional lower risk category (low risk, PQS only) is explicitly created, under which such applications can fall. Furthermore, as life cycle management of dossier is a significant burden to implementation of process models, the inclusion in the dossier of additional, PQS-like information for process models only is a hurdle. It can even have impact on supply when introducing such a model during post-approval lifecycle and global approval is planned. With reference to the several types of protocols potentially required already for medium-risk models, it is proposed to remove the reference to including these in the dossier, applying the learnings from previous concepts like "Design Space Verification Protocols", for example, which historically have been a disincentive to adoption of design spaces.

4.4. Cross-Program mRNA Process Models with Interpretable Machine Learning (ML), Moderna

A Moderna case-study using ML process models trained from historical data of prior mRNA sequences was presented with the intended application to support and justify accelerated process development of future new programs.

A large amount of process data has been collected from different programs at Moderna, making it feasible for the development of quantitative models that can be used to predict process performance of new programs. In the case-study, historical data from process development experiments are linked with mRNA sequence attributes to build a database of a variety of mRNA sequences. The data is then used to train interpretable ML models to predict process outcomes given new mRNA sequences. One of the potential challenges of this kind of cross-program ML models is the hurdle to justify the generalizability of such models when applied to new mRNA sequences. Several steps are taken to enhance the interpretability, and further the generalizability of these statistical learning models. Firstly, interpretable models are used instead of black-box models. This allows the sequence effects and process parameter effects to be decoupled in the mathematic forms of the models. The decoupled functional forms demonstrate universal correlation with process parameters independent of mRNA sequences, and therefore justify the generalizability of the models when used on new programs. In addition, an evidence layer has been added to give reasons of suggested range of process parameters with prior experiments to give example-based interpretability. It is believed the approach in the case-study provides strong justification of applying ML process models trained using historical process data

of a variety of sequences to predict process outcomes and determine design spaces for new programs *in silico* without extensive process characterization studies.

The presentation also suggested several additions to the Preliminary QIG Considerations regarding Pharmaceutical Process Models to solve the challenges when applying prior knowledge or process models in regulatory filings, such as providing harmonized performance metrics for mechanistic and ML process models in a single guideline, and providing tiered expectations of explainability based on the model impact and risk in applicable guidelines. In the current submission framework, it is challenging to include prior knowledge and process models from other products in the dossier for review. It is therefore suggested to encourage deep-dived forums, regulatory agency sponsored research, or any other mechanisms to increase the understanding on the topic to simplify the adoption of ML and process models to accelerate process development.

5. Summary of the discussions

Stakeholders welcome the publication of QIG's preliminary considerations guidance document and the LLFG meeting as an initial crucial step to address current regulatory challenges associated with the use of process models, providing principles and a framework.

It was noted that there are different documents in the public domain related to pharmaceutical process models and it would be beneficial if the QIG document could include some **definitions** and provide reference to existing guidance, when appropriate.

The different case-studies presented during the LLFG gave an outline of the diversity of models in pharmaceutical manufacturing. Some comments received during the public consultation on the QIG preliminary considerations suggested to further specify the regulatory expectations as a function of model type. In order to follow up on this and better understand stakeholders' needs QIG asked the audience their views. Given the variety of models, there was general agreement that an **agnostic regulatory framework**, able to accommodate the different types of models and approaches that may be used in the future, would be preferable. Nonetheless, the individual characteristics of the model and the risk of the model to the product quality are to be considered on a case-by-case basis. In that respect, some interesting features were underlined by the speakers. For instance, regarding mechanistic models, the necessity to give confidence in the assumptions and their relevance in a specific process was stressed. This allows fully embracing the power of the mechanistic models. The importance of prior knowledge and engineering judgment was recalled, as well as the usefulness of peer-reviewed scientific literature. If a model includes a mechanistic part and an empirical part, the biggest validation effort should be put on the less known component. Assessment should focus on the validity domain against the context of use, and on the prediction accuracy within the validated ranges.

There was consensus that the **level of risk of the model defines the dossier requirements and lifecycle management expectations**. It was understood from the discussions that the majority of stakeholders were used to dealing with impact categorization (as per ICH Q8/Q9/Q10 Points to Consider) instead of risk categorization, but no strong preference for one or the other was taken by stakeholder participants. QIG explained the added value of considering risk, in that risk considers the role of the model in the overall control strategy as well as the additional, potentially mitigating, control strategy elements. As such, it can be viewed as a more holistic categorization than only considering the model impact. QIG acknowledged the necessity to further elaborate on the link between impact and risk in the guidance. Another suggestion from stakeholders was to open the ICH Q8/Q9/Q10 PtC for revision, but this is an ICH document and goes beyond QIG control. During the discussion, it was agreed that models predicting non-critical quality attributes should not lead to medium or high-risk model categorization. Risk evaluation should thus consider the criticality of the predicted attribute. Interesting considerations were brought forward about risk being a continuum, thus sometimes leading

to subjective interpretation at the time of classifying models into three levels (low-medium-high risk). The discussion emphasized the importance of the continuous assessment of risk during model lifecycle and the rigorous evaluation of the acceptable level of model uncertainty depending on the context of use.

- The case of **models deployed in GMP setting only**, was briefly touched. QIG acknowledged the use of models in GMP for internal process monitoring only, as an additional layer of control but taking no action in the decision-making process or no decisions that impact material quality or disposition. The QIG explained that for those models no information is expected in the dossier, and such models can be managed under the PQS.
- QIG clarified that, as indicated in the QIG preliminary considerations document, 'for **low-risk models,** provision of a high-level discussion regarding model use is sufficient'. This is in line with the ICH Q8/Q9/Q10 Points to Consider document, which for low impact models requires a discussion of how the models were used to make decisions during process development. Proposals from stakeholders for optional description in case of low-risk models were received.
- QIG also took the opportunity to clarify that most of the requested model information for **medium-risk models** referred to in the QIG document is to be provided in the development sections of the dossier (3.2. S.2.6 and /or 3.2. P.2.3) (not in 3.2.S.2.2 and/or 3.2.P.3.3), so that it is part of the process development story providing sufficient information to the assessor to understand the product/process. Stakeholders welcomed this clarification and the fact that the focus should be on providing an outline of the model development and its intended use rather than model-specific details including complex datasets.

Whereas the **classification of models** as low or high risk and the associated regulatory requirements are generally clear, the **medium risk category** triggered some discussion, especially with regards to their description and validation requirements, as experience is limited. To address this, QIG encourages stakeholders to engage in early discussions on their model(s) with them. Pre-submission interactions can facilitate a better understanding and alignment between the applicant and regulators, complementing the information ultimately included in the dossier. The learnings from those examples will also inform guidance development.

Discussion on dossier content continued with the topic of **model maintenance during lifecycle**, which is perceived as the major challenge. The following remarks were made:

- Stakeholders advocated for the majority of the changes to be managed under the PQS. The rationale for that is the need for an agile system in order to continue bringing innovation into the manufacturing floor. Industry pointed out that, as models get deployed in manufacturing settings, they become part of standard GMP protocols and processes. Provisions of the PQS for change control are thus applicable as already existing for computerized systems and GMP processes in general. However, it is fair to say that there will be some areas where for a specific model, particularly high-risk models, there will be a need to communicate to regulators the evolution of the risk, which performance attributes will be focused on, to make certain changes clear and transparent, to inform when there will be notification and when not, etc.
- Again, it was acknowledged that having a one-size-fits-all regulatory pathway to deal with model changes is hardly conceivable. QIG recognized that flexibility is desirable.
- As part of the review of the stakeholder comments from the public consultation and the presentations at the LLFG, QIG noted that there had been some misunderstanding regarding its vision of model lifecycle management. Question 4 of the QIG preliminary considerations refers to the submission of a **model maintenance protocol** in 3.2.R. for medium and high-risk models. The intention of such a protocol is to describe and agree with the regulators how

the potential changes to the model that may occur during its lifecycle and their consequences will be handled post-approval (i.e., set the conditions for changes that can be managed within the PQS or require submission of a variation). QIG clarified that the advantage of using such a protocol, instead of a traditional post-approval change management protocol (PACMP), is that it would allow for some changes to be made under the PQS, and not require the submission of an implementing variation (which is necessary for PACMP). The proposal in the QIG preliminary considerations document for having some sort of lifecycle protocol was thus essentially an option to offer more flexibility to manage changes for high-risk, and case-by-case medium-risk, models. This should be viewed as a tool to make communication happen and a place for proactive negotiation at the time of model registration. Stakeholders welcomed this clarification. In this regard, there seemed to be some confusion between these protocols (PACMP/proposed model maintenance protocol) and the (continuous) model verification protocols. PACMP/proposed model maintenance protocols are intended to define the regulatory lifecycle management expectations (potential post-authorization changes and how these will be handled under the PQS or via variation, including the reporting category). The (continuous) model verification protocols are used to (continuously) check whether the model is performing as expected and trigger model rethinking/retraining when needed (ref. CHMP Guideline on process validation for finished products - information and data to be provided in regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1) and therefore have a different scope.

The discussions led to an important reflection around **model uncertainty quantification, or sensitivity analysis**. It was acknowledged that **uncertainty quantification is essential to validate whether the model is suitable for a defined context of use**. The concept of total uncertainty through error propagation, was emphasized as a powerful tool to determine the risk associated with the use of a model.

- Whether requested or not in the regulatory submission, depending on the use of the model, uncertainty quantification is part of model validation good practice.
- For low-risk models higher levels of total uncertainty could be accepted compared to high-risk models where lower levels of total uncertainty would be expected.
- QIG asked the audience their views on a comment from a stakeholder received as part of the public consultation on the QIG preliminary considerations document, which suggested the inclusion of a performance metric table (similar to that used for analytical method validation) in the QIG document, and also sought their views on which parameters should be included and why, and what would be the reason(s) for a certain type of model not to address a certain parameter. Heterogeneity and complexity of models was pointed out, making it difficult to have a one-size-fits-all approach covering all metrics for all types of models. In addition, this field is in constant evolution and new methods are emerging regularly. While for certain established group of models there are some metrics generally used, ultimately it is a case-by-case decision and inclusion of such a table would be too prescriptive. Several stakeholders' comments were in favour of keeping this high-level in the QIG document, and leaving up to the applicants the responsibility to justify their selection of specific metrics.

Communication of information on models to regulators was debated in depth during the two days panel discussions.

- There was consensus that the transparency about the role of a model, the fitness for purpose and credibility of a model for that purpose, is what has to be conveyed in a way that is understandable for regulators so that they gain trust into the model.

- Some stakeholders proposed to submit information/ validation/ lifecycle summaries instead of detailed reports.
- The importance of comprehensive SOPs to guarantee model credibility, was emphasized. A stakeholder proposed to proactively open up internal documentation of the PQS in order to show regulators how they are working.
- The value of scientific publications was highlighted, so that information on innovative manufacturing approaches become part of the general knowledge space.
- The value of pre-submission interaction was also emphasized. Opportunities to discuss with the companies and follow-throughs, to make assessors and inspectors familiar with the applications, could greatly facilitate the process before models become common practice. The need for an on-going dialogue was agreed by all participants.
- Stakeholders expressed the need for a threshold for disclosing information on models in the dossier. They consider not all model information is relevant for assessment, but only information for models having an impact on the control strategy. Regulators pointed out the need to understand the rationale behind the risk evaluation to agree on the level of detail expected in the application depending on the context of use. When a model is part of the control strategy of a medicinal product, whether is low, medium, or high-risk, then communication on the risk evaluation becomes crucial. If not properly conveyed, this could lead to unnecessary questions from the regulators.

Another comment received during the public consultation suggested to further elaborate on the **requirements for ML/AI** in manufacturing. Participants believed that data-driven models like ML models are part of the same framework as other process models. The existing guidance is then sufficient, and the community should focus on developing standards and best practices to facilitate practical implementation. Indeed, how to qualify ML and data-driven models is seen as the main gap today.

There was also some discussion on how stakeholders are intending to maintain self-evolving models within the PQS and communicate the updates to the regulators. Whereas the field is still progressing, initial thoughts were directed towards use of uncertainty and sensitivity analysis to incorporate the adaptations in the parameter space, constantly evaluating the predictions, and use the normal change control framework as needed.

- For some changes the model itself would be sufficiently robust; however, when changes are made outside the existing limits, a model update is likely to be required.
- The envisaged scenario of making updates offline as new data is collected, during the initial deployment of ML models, was evoked by one stakeholder in a stepwise approach. Those periodic updates would allow evaluating the key performance criteria to put in a protocol so that, in the end, updates could be kept under PQS.
- The effort for more transparency with ML/AI models was recognized. The important thing is that information and decisions are available and readily accessible to users of the model and regulators, properly documented and justified.

To further support the development of guidance, emphasis was put on the **need for examples from stakeholders** (practical examples of the content of a typical dossier summary, example of the content of a typical GMP procedures/protocols to manage models under the PQS, etc.) that can inform discussions.

QIG stressed that **early engagement** to ensure there is mutual understanding over the specificities of each case is key both for applicants and regulators.

QIG emphasised that it is not the intention to treat models differently to any other elements used in the control strategy. The level of detail to be included in the dossier should be commensurate with the level of information needed to ensure the assessor has sufficient understanding of the applicant's proposal. **Clear evidence that the model is fit for purpose and credible should be provided to give confidence to assessors and inspectors**.

6. Next steps

The LLFG meeting provided a good forum to discuss challenges and possible solutions in relation to the use of process models in manufacturing with industry and academic stakeholders, and to identify points that need to be further considered in the QIG Preliminary Considerations document. These include:

- Inclusion of a glossary
- Further clarification on the concept of model risk, focusing on the CQAs and making the link to the risk to the patient
- Clarification that models used for internal process monitoring ('shadow mode') purposes only, as an additional redundant layer, and take no action in decision-making can be managed under the PQS, no information is expected in the dossier.
- Further reflection on the regulatory expectations for medium risk models, including clarification that the model description is to be included in the development sections of the dossier (3.2.S.2.6. and/or 3.2.P.2.3).
- Further reflection on model lifecycle management

To further support stakeholders with the implementation of process models and the development of regulatory guidance, applicants are invited to request a 1:1 meeting with QIG to discuss their proposals. Practical examples of how QIG considerations are applied to specific use cases (e.g. content of a typical dossier summary, content of a typical GMP procedure/protocol to manage model under PQS), will help foster mutual understanding of regulatory expectations and consider case specificities. These concrete examples will also help develop build experience in the application of models and contribute to the development of guidance and future training of EU assessors and inspectors.

European Medicines Agency

Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Telephone +31 (0)88 781 6000
Send a question www.ema.europa.eu/contact

www.ema.europa.eu

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