EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2024
EMA/455426/2023
Human Medicines Division

Meeting Report

2nd Listen and Learn Focus Group (LLFG) meeting. Quality Innovation Group (QIG)

12th-13th October 2023, Hybrid (Webex)

Introduction

Following the 1st QIG LLFG meeting on 13th March 2023, the QIG organised its 2nd LLFG meeting on 12th and 13th October 2023. The scope of this meeting was to discuss with stakeholders the application of digital novel technologies to manufacturing and quality control testing; in particular process models and digital twins, as well as artificial intelligence (AI) and machine learning for GMP applications. This is in line with QIG priority topics for 2023, as described in the 2023 QIG workplan.

The objective was to identify and understand the stakeholders' challenges with the development and implementation of these technologies, to proactively formulate appropriate regulatory responses to them as they become mature (e.g., developing position papers, Q&A documents, etc.); support their development and implementation; and ensure EU harmonisation as well as global alignment. Although some challenges have been identified from previous interactions with industry and literature review, further dialogue with stakeholders was required to fully understand the specific quality and GMP challenges they face.

A call for abstracts from stakeholders on the proposed two topics was launched in July 2023 to identify specific focus areas for these priority topics to be discussed during the meeting. The QIG considered all 27 abstracts submitted by industry and academia and selected the ones to be presented at the LLFG. The aim of these presentations was to describe the proposed technologies, including their maturity and to point out the perceived scientific and regulatory challenges with the current EU regulatory framework from the stakeholder's perspective.

The event was attended by QIG members and secretariat, 57 industry participants, 16 academics, 42 regulators from the national competent authorities, as well as partner international regulatory authorities, including US FDA and PMDA representatives.

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The meeting comprised the following sessions:

Thursday, 12th October 2023

1. Introduction to QIG, meeting scope and objectives of the 2nd LLFG meeting
2. Presentation on Enabling Technologies in regulated Pharma by ISPE
3. Session 1 on Process models, digital twins

    3.1. Presentation on Advanced Digital Control Concepts for continuous manufacturing (CM) processes, RCPE

    3.2. Presentation on End-to-End Digital Twins for Process Control, Körber Pharma

    3.3. Presentation on System Modelling Applications for Pharmaceutical Process Development, GSK

    3.4. Presentation on combination of computational fluid dynamics derived compartment models with biological kinetic models for fast development, scale up and control of vaccines manufacture, Inno4vac

    3.5. Presentation on model-based process development and operation, DataHow

    3.6. Presentation on AI and digitalization technologies applied to ATMP manufacturing, AIDPATH

    3.7. Plenary discussion on Process Models and Digital twins

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

Friday, 13th October 2023

4. Session 2 on Artificial Intelligence, Machine Learning for GMP applications

    4.1. Presentation on Frame-by-Frame Risk Profiling Technology, Moderna

    4.2. Presentation on Automated Reading of Agar Plates using AI, AstraZeneca

    4.3. Presentation on Chromatographic Peak Integration using AI, Merck KGaA

    4.4. Presentation on Visual Inspection Robot with Machine Learning Algorithms, Roche

    4.5. Plenary discussion on Artificial Intelligence, Machine Learning

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

5. Next steps

The next sections of this report summarise the discussions and key points raised by industry and academia stakeholders during each of the sessions. The stakeholders' identified challenges and proposed solutions for Process Models and Digital Twins and Artificial Intelligence and Machine Learning for GMP Application are also highlighted in the conclusion section of this report. While it is emphasised that these are the views expressed by stakeholders, the QIG took note of these and outlined some areas for future follow-up as presented in sections 3.8 and 4.6 of the report.

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.

QIG priority topics in 2023 were continuous manufacturing (CM), decentralised manufacturing (DM) and automation/digitalization of processes. The first two priorities were the focus of the first QIG LLFG held on the 13th of March. This second QIG LLFG in October 2023, summarised in this report, focused on process models and digital novel technologies.

The objective of the LLFG was to gather information from stakeholders, both from industry and academia, on their developments in these areas, the regulatory challenges they face and their proposed solutions to overcome those. These will inform the identification of the follow-up actions required at EU level to support the development and implementation of these technologies.

2. Presentation on Enabling Technologies in regulated Pharma, ISPE

ISPE presented a summary from their latest survey on Pharma 4.0 TM (2022), based on 10 questions, 400+ anonymous answers from 57 countries around the globe. The questions concerned the digital maturity level, enabling technologies adoption, benefits, and challenges. Key benefits are expected in quality & compliance, efficiency increase and time & cost savings. The analysis highlighted that most of the companies are still at the beginning of the Digital Transformation journey, with only a slow progression towards a higher maturity level. Shortage of resources, skills/competences and basic technologies required are described as internal challenges, that slow down the development. A detailed overview was presented from what emerged from the analysis of the 35 selected and structured Case Studies on Pharma 4.0 TM, identified among the 300 eligible within the ISPE body of knowledge.

Following enabling technologies have been identified and it was highlighted that these could be required to be implemented in parallel to make them successfully operational: GxP Cloud, Smart and Wearable Devices, Collaboration Platforms, Big Data and Advanced Analytics, Industrial Internet of Things, Artificial Intelligence / Machine Learning (AI/ML), Process Mining, Natural Language Processing, Image Recognition, Advanced Modelling, Advanced Robotics, Augmented Reality, Virtual Reality, Additive Manufacturing, Robotic Process Automation, Blockchain, Speech and Gesture Recognition, Edge Computing.

A few lessons learned were emphasised by developers*:*

- The community still needs to enable trust and user acceptance in innovative tech like AI/ML/Advanced Modelling, here a respective expertise needs to be fostered in the companies and academia developing these technologies.
- The concerned organisations need to build up the adequate culture, including the respective technical, business, organisational skills, to ingest, analyse and properly use vast amount of data.

- It is essential to embrace the early education and involvement of the whole project team. Here an excellent and precise communication between the experts of the sub-disciplines (including interdisciplinary experts) enabling a certain technology is considered indispensable.

- Cybersecurity is one of the basic requirements that needs to be evaluated from very early on.

ISPE also reported a selection of requests from ISPE members on the 'regulatory challenges in implementing novel digital technologies':

- A clear and harmonised regulatory definition of AI (and other novel tech) to be used in ' regulated ' pharma.

- Globally harmonised regulatory requirements for AI and associated novel technologies application in pharma.

- A primary guidance for the implementation of such innovative approaches, that includes reference to all available principles for GxP and describes the responsibilities of human beings in the digital environment of manufacturing and quality.

- Suggestion to create and share the 'Aide memoires ' for GxP inspectors with the Industry & Vendors to guide interpretation of compliance to GxP for innovative technologies.

- Which level of process understanding is expected for applying novel technologies?

- Regulation should focus on principles, not on operational and technical details.

3. Session 1: Process Models and Digital Twins

3.1. Advanced Digital Control Concepts for CM processes, RCPE

The presentation, 'Advanced digital control concepts for continuous manufacturing processes,' proposes a workflow for designing Quality by Control (QbC) methodologies on industrial-scale equipment established at the Research Center of Pharmaceutical Engineering (RCPE).

QbC algorithms involving novel soft-sensors (providing real-time data), control, and human-in-the-loop algorithms were designed and tested by RCPE on the industrial manufacturing line ConsiGmaTM-25, a 'from powder to tablet' continuous manufacturing line.

The aim of this real-time data-driven control concept is to discard out-of-specification material from the production stream in an early production stage. Moreover, the process parameters are adjusted in order to reach the target (intermediate) critical quality attributes (CQAs), like (e.g., model predictive controller for granule size). In the proposed concept, human-in-the-loop algorithms that rely on fault detection algorithms and provide meaningful suggestions/messages for the plant operator, are considered central. Besides this, following essential requirements for the described integrating QbC concepts have been established:

- In-line process analytical technology (PAT) equipment for real-time monitoring of the active pharmaceutical ingredient (API) concentration in wet granules and the particle size distribution (PSD), based on neural network (NN) data-driven process models linking the ConsiGmaTM-25 process parameters and the granule size. Soft-sensor for real-time prediction of loss-on-drying based on the physical laws describing mass- and energy balance equation within a fluid-bed dryer.

- Soft-sensors based on machine learning (ML) for predicting a tablet dissolution profile from the process data.

The preliminary design of the proposed algorithms was performed in the simulation environment. The algorithms were then tested and fine-tuned on the real system. After the prototype versions were created, algorithms were integrated into a cognitive automation platform (CAP), i.e., a FIWARE-based open-source framework for process industry digital transformation. Finally, the performance of the proposed algorithms and CAP platform was evaluated through selected disturbance scenarios performed on a ConsiGmaTM-25 manufacturing line. The obtained results were compared to standard ConsiGmaTM-25 operation (in absence of the QbC algorithms), and the improvement in terms of disturbance robustness and waste amount was observed. The proposed digitalization platform (CAP) was tested for efficient data employment and virtual operator training.

Upon developing these concepts and aiming to integrate them as standard components in industrial production facilities, the following challenges were identified:

- Although the existing regulations clearly outline the requirements and criteria for the final product quality, information related to the intermediate product remains unclear. For instance, it was not clear whether the definition of tolerances (%) for a quality control concept that employs monitored wet granules CQAs (e.g., size) to discard material was not straightforward.
- The selection of the experiments and the necessary amount of data validating models and model-based control strategies were individually defined by RCPE. Some guidance to support this procedure would be helpful.
- Guidance on model lifecycle management (e.g. due to incoming variability).

3.2. Process Control: End-to-End Digital Twins, Körber Pharma

End-to-end process models were presented as an essential tool applying the ASME V&V40 credibility framework (that provides a risk-based framework for establishing the credibility requirements of a computational model) to verify and validate process models. End-to-end models are developed with the aim to enable risk informed predictions of final product quality as a function of process parameters (PP) of individual unit operations. Based on these model predictions product quality can be directly assessed in view of drug substance and drug product specifications, relevant for patient safety and efficacy. This is considered as an advantage of end-to-end process models over process models predicting individual unit operations. A central approach to rate applicability and credibility of models within the V&V40 framework is to compare the model including its uncertainty to acceptance limits. The presentation showed how end-to-end process models can (1) correctly account for sources of variability in uncertainty quantification and (2) how to overcome the necessity to define acceptance limits for intermediate process steps.

1. For uncertainty quantification Körber presented two major sources of uncertainty that need to be quantified during process modelling: *epistemic uncertainty*, quantifying structural and parameter uncertainty, as well as *aleatory uncertainty*, e.g., inherent analytical and process variance. Addition of experiments to model training will reduce the level of epistemic uncertainty converging towards 0, whereas aleatory uncertainty will converge towards the true inherent analytical and/or process variance. Historically only epistemic uncertainty was used to assess the uncertainty of a model, e.g., only confidence intervals for the prediction, which is heavily over optimistic to rate future process performance. Sound modelling approaches need to account for both uncertainties, which can be realised by using tolerance intervals for the prediction instead of confidence intervals. In addition to using the right uncertainty interval, end-to-end process models, implemented as Monte Carlo simulations, enable to propagate the uncertainty of inputs (e.g., process parameter settings as well as material attributes) together with the epistemic and aleatory uncertainty of the model through all unit operations to receive is risk informed prediction of final product quality.

2. Körber presented the following concept for establishing acceptance limits. For models covering intermediate process steps, acceptance limits of product quality are not known a priori. As a workaround to account for the missing acceptance limits modeller and process scientists have historically chosen arbitrary limits of x times the standard deviation (SD) of existing data to establish those acceptance limits. There are two major drawbacks of such an approach (1) the choice of x (2, 3, or 4, etc.) is arbitrary and (2) it favours to have large process variability as this approach will lead to large acceptance limits. End-to-end process models overcome this limitation as a direct link of any process parameter of any intermediate process model onto final product quality is possible. At that stage drug substance specification can be used as acceptance criteria, that are relevant boundaries for patient safety and efficacy.

The end-to-end process models have been presented as a solution to assess whether sufficient data-based evidence of a process been gathered, including a full understanding of uncertainty/risk about the concerned process inputs and process models, and to substantiate the claim that there is sufficient process understanding to consistently deliver the required product quality to patients.

3.3. Application of Process Systems Modelling for Pharmaceutical Process Development and Manufacturing, GSK

Two case studies highlighting the application of process system modelling (also known as integrated flowsheet models) and perceived regulatory challenges and potential solutions were presented.

Process system models are composed of a series of interconnected mechanistic (knowledge-driven), empirical (data-driven) or hybrid models that describe individual unit operations of the manufacturing process of a specific drug, including vaccines. These models can be used to simulate the behaviour of the entire manufacturing process and provide an end-to-end, knowledge-driven understanding of the impact of process parameters belonging to different unit operations of the manufacturing line on in-process and/or final product critical product quality attributes (CQAs). As an introduction, the key aspects of mechanistic, empirical, and hybrid models were highlighted to emphasize the importance of distinguishing these models in any regulatory framework. The first case study described the use of a system model for a dry granulation platform. This knowledge-driven (mechanistic) model was applied to identify process parameters and input material properties that significantly impact product quality. Moreover, it enabled to determine process operating conditions to achieve consistent and robust product performance. During the presentation, the model's amenability for platform uses and limited need for product-specific data to confirm model credibility, was highlighted. The deployment of this model lead to a significant (>60%) reduction in laboratory experiments to establish optimal process setpoints and operating spaces.

The second case study described the development and use of a system model for an API continuous manufacturing process. This model was used to identify "most-forcing" conditions with respect to CQAs and process-derived impurities, to assess and rank process parameter criticality, to optimise process yield, and support transfer of the manufacturing process to commercial manufacturing.

Per the ICH Q8/9/10 Q&A points to consider guideline GSK would categorise the described models as "low impact". In combination with their mechanistic classification, the models require only little update or maintenance and data governance. They are, therefore, readily explainable, and amenable to platform use.

During the presentation the cases for broader use of low impact process systems models were highlighted to reduce traditional wet experimentation and provide more robust product and process understanding and control strategy development. These models will further support enhanced or

performance-based approaches under ICH Q12. Perceived regulatory challenges for process systems models and proposed solutions were also presented. These included:

- The challenge on the uncertainty on whether regulatory agencies would accept a given mechanistic model. A solution proposed was to create a database or registry for developers and the agencies of well-established mechanistic models.
- The lack of clarity on the requirements for credibility or verification of low/medium impact models in filings. The proposed solution was to specify in guidance that these elements are e.g. PQS by first intent.
- The 3rd challenge identified was the relevance of requirements or expectations (both for regulatory files and GMPs) for AI/ML models, with the proposal to develop clear guidance that primarily differentiates regulatory expectations based on model class and impact.
- Other challenge is the limitation of mechanistic models based on AI/ML based considerations (e.g., limiting extrapolation), suggesting outlining limitations and advantages of each model class in guidance, and considering the use of post-marketing agreements, if needed.
- GSK also identified as a challenge that the clinical phase-based requirements are unspecified and suggested clarifying the minimal expectations for models used in Phase I - III studies.
- The last challenge reported was regarding the requirement of additional wet experimentation, which is exacerbated by extensive global assessments. On this point the proposal was to facilitate pre-alignment on required experimentation or datasets, and potentially create avenues for joint global assessment or pre-alignment.

3.4 Combination of computational fluid dynamics derived compartment models with biological kinetic models for fast development, scale up and control of vaccines manufacture, Inno4vac

The Inno4Vac consortium addressed in their presentation how a compartment model (CM), classified as mechanistic/knowledge-driven model, can be derived from a Computational Fluid Dynamics (CFD) model. The advantage of the CM is their lower computational burden, compared to the CFD model. Their overall aim is to speed up vaccines' process development, scale-up/down and enhance process understanding (e.g., bioreactor dynamics).

The basic principle is that each compartment in the CM corresponds to a volume within the bioreactor which has equal physical behaviour. The CM is then validated based on a simple mixing experiment (pulse addition of a tracer, for example acid or base pulse addition with pH sensors installed at different locations in the bioreactor for data collection) where the CM should be able to reproduce the data collected in a mixing experiment. A comparison of modelling results at different scales is used to verify that the model can predict heterogeneity inside the reactor at different scales. This validated CM "Prior knowledge" can be reused for any process using the same equipment size and configuration.

The developed CM is proposed for independent use and/or in conjunction with the Kinetic Model (KM, mechanistic/data-driven model, under development) to predict the behaviour of production bacteria within a bioreactor that might, for example, be linked to growth and antigen expression. The proposed kinetic cell model is a hybrid model, integrating both knowledge- and data-driven components. The knowledge-driven aspect is anchored in the metabolic network's structure, ensuring the model accurately mirrors mass and elemental balances, thermodynamics, and the general dynamics of uptake, secretion, and growth kinetics, encompassing phenomena like exponential growth and substrate limitations. Data are utilised for model reduction and parameter identification by embedding

knowledge-driven models into function approximators, such as artificial neural networks. Techniques derived from statistical learning, including Bayesian ensembles, are commonly employed to infer the reduced model from data, quantifying model uncertainty in the process.

For model verification, independent test experiments are undertaken at lab or pilot scale to evaluate the model's predictive accuracy. The overall data set for model verification is developed based on risk assessment and includes consideration of any adaptations to scale and equipment for commercial manufacture.

The CM, KM and hybrid (i.e., CM+KM) models are proposed to support product/process development/understanding. These models will not replace the product control strategy i.e., the CQAs will be controlled as part of batch release. Therefore, based on current ICH Q8/9/10 Points to Consider, the Inno4Vac is considering their models to be classified as low/medium impact models.

One challenge pointed out by Inno4Vac was the lack of current guidance on how to define model credibility for low and/or medium/low impact models. Therefore, the team proposed as a solution consider the definition of "credibility" as per ASME V&V40-2018 Assessing Credibility of Computational Modelling Through Verification and Validation: Application to Medical Devices.

The second highlighted challenge was the lack of guidance on the required information to be included in the dossier based on model impact. Therefore, the proposal for the dossier was to include only a short discussion on how the model(s) is used to make decisions during process development i.e., scale-up/down optimisation, and the model(s) assumptions and performance, considering that the Inno4Vac models are classified as low and/or medium/low impact. Based on the current experience it was suggested that no explicit filing and subsequent maintenance of algorithms/equations is to be included in the dossier, and that periodic model CM+Kinetic verification could be managed via the Companies' Pharmaceutical Quality System (PQS).

It was highlighted by consortium that it is considered important to develop a harmonised, global guidance and/or update existing guidance (e.g., ICH), to standardise the terminology and methodology for process modelling, define regulatory expectations for dossier content based on model type and impact, including details on the requirements for assessment of model credibility/verification, and define which changes can be managed via the PQS.

3.5. Model-based process development and operation, DataHow

The routine application of modelling in process development and manufacturing demands well-defined workflows for concurrent model and process development, as well as a clear approach to leverage modelling insights, particularly when product quality might be affected.

Using an upstream mammalian cell culture process as an example, DataHow introduced their standardised workflow for model development and application. The workflow begins with data visualisation and variability assessment to understand the inherent limitations of the data. Subsequently, they employ a standard mammalian cell culture hybrid model, which combines generally valid material balances with machine-learning models to estimate unknown biological rates. A bagging approach is used, aiming at reducing potential biases in data selection for training and validation. This approach was shown to be successful in predicting culture evolutions, as also evidenced by various past projects. Moreover, DataHow suggested to use a separate historical modelling approach to model critical quality attributes, which, as demonstrated in an example, outperforms the currently widely used response surface models. Model quality is assessed using standard performance criteria on both training and test data, (the latter not being used for model training). Additionally, visualisations are

employed to identify issues that may not be reflected in the criteria, such as functional biases stemming from incorrect feeding information.

To handle uncertainties, especially regarding the machine-learning models perceived as the weakest component, a validity measure is used to evaluate how far new process conditions deviate from the observed conditions on which the model was developed. The concept is that model predictions for conditions significantly outside the validity domain carry a higher chance of inaccuracy, i.e., "the model is less valid predicting on those scenarios it was not trained for". Application of the concept in process scale-up and process characterisation were presented, where data generation is expensive. It was highlighted that a greater reliance on the model's predictions could reduce wet-lab experimentation while enhancing insights into process behaviour. However, if using in-silico results for regulatory submissions, it is crucial to consider the questions agencies may pose regarding model quality and validity as well as the risks to product quality. DataHow advocated for an "A-mAb alike study"[1] for model-based process development and operation, aiming to provide a concrete example of how expectations for filing regulatory documents could be fulfilled.

3.6. Presentation on AI and digitalization technologies applied to ATMP manufacturing, AIDPATH

AIDPATH (Artificial Intelligence-driven, Decentralised Production for Advanced Therapies in the Hospital) is an EU consortium, dedicated to enabling and augmenting the next-generation of personalised medicine using artificial intelligence (AI) combined with process automation technology. The AI based automated technology is developed to enable manufacturing with gene-engineered immune cells at EU hospitals applying artificial intelligence (AI) technology. The presenters pointed out that, AI combined with process automation technology, has the potential to increase the efficiency and the quality of engineered cell therapy to a point that equals or exceeds what can be achieved with centralised manufacturing. AI approaches also have the potential to substantially increase the personalization of therapies through deep learning and the use of digital twinning concepts.

3.7. Plenary discussion on Process models and Digital Twins

Stakeholders presented a variety of different model applications and their perceived challenges and opportunities, which provided insights into user considerations, potential regulatory hurdles, and proposed solutions to overcome these.

In view of the presentations, QIG asked the speakers what major regulatory and scientific challenges can be expected in the development and implementation of models and what considerations should be made in advance. The following were identified:

- Industry pointed out that a clear identification of the context of use of a model is a prerequisite for any model development process; all subsequent considerations, including model risk, follow from that starting point.
- Industry also mentioned the need for cross-functional diversity in development teams, to cover aspects such as verification of model performance and evaluation of data, and the potential hurdle of data integrity and data security. The importance of timely involvement of not only scientific staff but also regulatory/quality staff was highlighted.

[1] Exemplary: A–Mab: A Case Study in Bioprocess Development, 30 October 2009, CMC Biotech Working Group.

- When developing models, data are a crucial issue. Stakeholders stressed the importance of data source, data relevance (have all impactful parameters been considered?), data accuracy, frequency of collection, etc., always keeping the application in mind.

Regulators asked whether changes in the traditional regulatory validation approach may be required when it comes to complex models e.g., AI models. It was agreed that the demonstration that a model is fit-for-purpose cannot be done using a static approach. Establishing a plan for continuous model validation and maintenance would be a desirable strategy. Industry acknowledged the need for a change in the traditional validation approach for certain technologies that use for example big data or AI/ML algorithms. Industry stressed that regulatory requirements on data for the validation, but also on the expected documentation, needs to be discussed and defined for the new types of models that are being developed. For example, even though cross-validation may be performed, the risk of having a biased test data set should not be underestimated. A proposed solution to overcome this was to produce the test data set after the claiming of the fit-for-purpose status in order to improve the confidence in the model. In addition, some participants indicated that guidance should ideally also cover the requirements for accuracy parameters for model validation, whereas others asked for not prescribing any particular performance metrics.

If a design space has been approved for a process, industry claimed that submission of data for validation and verification of models, while moving within the approved design space, should not be required as part of the Marketing Authorisation Dossier. The approach of not submitting further model information to regulators while operating within an approved design space, if this model was initially proved to be fit-for-purpose, was overall deemed a reasonable approach and in line with current regulatory expectations as described in ICH Q8.

It was emphasised that two aspects need to be considered for model implementation: establishing the credibility of each individual model in the context of use, and the overall process validation. With the use of AI/ML models, it was recognised that performing three PPQ lots under ideal target conditions will not necessarily provide encompassing data to entirely reflect the process like it will perform under real-life conditions. Therefore, e.g. the concept of continuous process verification, gathering data under real-life conditions, could be used to establish the process state of control while coupled with model monitoring. Ideally, validation guidance for models will involve such approaches, considering the characteristic of processes, that include models in process development.

Regulators re-emphasised that the approach for validation is not a one-size-fits-all, and that whatever the proposed strategy is, it should always consider the risk in the context of use. It was acknowledged that there can be limitations to the model use in the first phases of development and implementation, but this can be explained to the Authorities in the supporting risk assessment.

One stakeholder comment highlighted that "We should get the most out of the existing best practices in terms of model validation and documentation", e.g. from the field of spectroscopic modelling, so that implementation is not too much delayed by discussions that have already been held in the past.

In response to the regulators subsequent question as to which aspects are important and should be covered in guidance, industry parties referred to ASME V&V 40 on medical devices for establishing the basis for a framework for models in medicines. Industry also indicated the need for guidance on how to document low impact models, single use models and models used for development, in dossiers and in the PQS, and which GMP status should be assigned to them. Industry suggested that relevant information may be required in the dossier, but the changes to low impact models and the submission of these would ideally mainly be considered a GMP matter.

The question whether modelling could replace data requirements in a MAA as currently regulated by Directive 2001/83/EC Annex 1, was also raised by industry. QIG indicated that some modelling is

already being used and dossiers are being built as per current requirements. The use of AI/ML is still in early stages and regulatory requirements may mature in parallel.

On the other hand, other stakeholder's comment pointed out, that there is not necessarily a lack of available guidelines and standards which are considered sufficient, but rather the need for a more agile framework in view of current change control requirements. Indeed, QIG acknowledged that we should anticipate that models, data and processes evolve, so the practical deployment of models and their lifecycle should be facilitated in particular for high impact models which are expected to require more regulatory scrutiny.

Regarding GMP requirements, regulators referred to the on-going revision of GMP Annex 11 (Computerised Systems) and the already published EMA concept paper open for public consultation. Industry welcomed this revision as the gap in terms of AI/ML models is felt as a hurdle to their implementation. It was highlighted that the primary focus of the Annex 11 revision was to cover adequacy and integrity of test data, and the results and metrics of the testing. However, it was noted that the revision is still on-going, and implementation is not expected soon.

It was additionally highlighted by regulators that the opportunity of having an aide-memoire for GMP inspections (e.g., covering the critical points to be assessed during inspections) would supplement the current framework in a way that no major changes to existing GMP guidelines would be necessary (NB- this was further discussed on day 2).

To conclude the panel discussion, industry parties voiced their request for practical case studies.

Industry also voiced the need for direct interaction with regulating authorities to which QIG emphasised the possibility for stakeholders to request a dedicated follow up 1:1 meeting with the QIG to discuss specific aspects in more detail (including commercially confidential information).

3.8. General sum up on Process Models and Digital Twins

The final session of day 1 summarised the key take away messages from the discussions, including the challenges and proposed solutions for Process Models and Digital Twins presented by stakeholders during the meeting and the areas for follow-up.

For ease of reference, these points are summarised in the tables below.

Process Models and Digital Twins

Challenge 1

Currently there is uncertainty on the regulatory expectations for process models in terms of what information should be included in the dossier versus managed under the PQS with regards to validation approaches, model lifecycle management, etc. depending on e.g., model type, model impact and development status (MAA, CTA).

Proposed Solution

Develop specific guidance on process models, reflecting an approach which stands on the model risk in the context of the model use. Factors such as the role of the model in the control strategy, the frequency of additional monitoring, the model's performance, the potential consequence of an incorrect decision, the criticality of the manufacturing operation(s), and the intrinsic risk of the medicine, will be considered. The evaluation of the risk associated with implementation of a process model will be taken as the basis for any justification for inclusion of model related information in the dossier (e.g., model description, justification, validation data).

Process Models and Digital Twins

Overall, it was agreed that the data for a clinical trial application or marketing authorisation will likely contain an overview of the model validation, whereas raw data of the model will remain under the PQS and could be reviewed on site as needed.

Areas for follow-up

Develop guidance on modelling.

The stakeholders may come for a closed follow-up meeting with the QIG or EMA scientific advice, based on the status of their development, to present their approach and gain clarification on the regulatory expectations.

Continue and reinforce dialogue with international partners (e.g. US FDA and PMDA) to align expectations.

Challenge 2

Lack of a regulatory AI definition.

Proposed Solution

To create a regulatory definition, ideally internationally harmonised, drawing the line between AI and existing simulation modelling.

Areas for follow-up

Continue progress in the field and consider whether definitions included in EU regulations (e.g. EU AI Act) apply to pharma or a specific definition is required. This may, depending on the specificity, consider the different fields AI is used in the development of medicinal products (e.g. quality, non-clinical, clinical).

Challenge 3

Uncertainty in regulatory acceptance of AI applications in the development of medicinal products.

Proposed Solution

The EMA reflection paper on the use of AI in medicinal product lifecycle (EMA/CHMP/CVMP/83833/2023) outlines the basic regulatory principles. Overall, the acceptance of an AI approach will depend on the relevance of the provided data and justification in the context of use. Stakeholders are encouraged to seek scientific advice from the regulatory authorities to gain clarification on the regulatory expectations and acceptability of their strategy and data package.

Stakeholders can share experience with each other. The implementation of common quality standards for data, registries to share examples and certain data (e.g. validation data) between developers is proposed.

Areas for follow-up

Participating stakeholders may apply for a closed follow-up meeting with the QIG to discuss their approach.

Challenge 4

The validation approach for manufacturing processes using AI/ML is to be defined and does not fit into the classical pathway.

Process Models and Digital Twins
Proposed Solution Currently, to be defined case-by-case risk-based justification for each model validation. But overall, there has been consensus that the impact of the applied AI/ML model on the products safety and/or clinical stage of development will determine the required validation approach (considering quality and number of training, validation and test data sets). Guidance on the risk assessment/classification of an applied AI/ML needs to be developed as experience evolves. **Areas for follow-up** The stakeholders may apply for a closed follow-up meeting with the QIG or EMA scientific advice, based on the status of their development, to present their approach and gain clarification on the regulatory expectations.

4. Session 2: Artificial Intelligence and Machine Learning for GMP applications

4.1. Frame-by-Frame Risk Profiling Technology, Moderna

Moderna is piloting a technology known as "frame-by-frame risk profiling" to assess risks associated with manufacturing steps in their platform technologies. Using this technology and focusing on the aseptic manual vial filling process (in the individualised neoantigen therapy (INT) area), analyses specific "frames" or subprocesses for potential failure modes, assessing their impact using a metric called "Weighted Error Criticality" (WEC). Moderna has been collaborating with a third-party vendor to implement their "frame-by frame risk profiling" technology, also merging Virtual Reality (VR) technology with training expertise. This approach allows for auto-generation of clear documentation and training materials, including Standard Operating Procedures (SOPs) and Work Instructions (WIs), quality assurance oversight guidelines, process flow charts and process videos, and a risk profiling database. The method also suggests more efficient alternative processes, reducing first the risk with potential reductions in processing times. The technology also addresses the issue of training, which traditionally poses challenges due to the complexity and high-risk nature of the cleanroom environments and manufacturing processes. The frame-by-frame risk profiling technology enhances training by harmonising/developing consistent training materials with deeper and clearer understanding of the 'why', 'what' and 'how' of the process along with the associated risk. The potential benefits of this approach include reducing time to qualification for operators, while reducing human errors and deviations. The technology also allowed for the reuse of frames in different procedures, saving time and resources. The following challenges were identified while implementation of this technology. Validation and recognition versus the accepted Failure Modes Effect Analysis (FMEA) could be a challenge in statistical analysis. There could also be potential scientific challenges from reusing the frame for the risk profiling for other processes. Additionally, potential barriers in current EU legislation could be the lack of guidance toward usage of software to automatically generate risk assessments and cultivate documentation and training material for personnel. The proposal to overcome these challenges, is clarification in 'what' and 'who' is responsible for the generation of 'training' and whether software and automation is appropriate over developed manually. The technology and its alternative approaches shall be supported by data, proper rationale, and the frame-by-frame risk profiling.

4.2. Automated Reading of Agar Plates using AI, AstraZeneca

AstraZeneca presented on the use of AI to enable automated agar plate reading for environmental monitoring. Currently, plates are visually inspected to assess for the presence and quantification of microbial growth. The results are then manually added to computerised systems. This manual handling takes time and there are also variations in the way individuals count colonies. A more standardised and automated way of measuring is required. AstraZeneca's aim is to utilise a technology solution that has been established in the clinical microbiology space and achieve a successful Proof of Concept within AstraZeneca for the application of environmental monitoring. Once the technology is formally optimised, developed and validated, the intention is to deploy to the sites across the global network. The instrument is an automated plate reader that uses a camera system and machine learning model to count and sort plates. The model has been developed using large data sets of a range of 90 mm agar plates. The model has been trained to identify microbial growth and ignore other components such as non-microbial artifacts. The model will be fixed after validation and will not actively machine learn after deployment. The plate count will be directly transferred into a GMP data system. Data trending, result review and release will be performed in the data system. One challenge identified is the question which of the individual plate images need to be retained. Transferring all the images over to data system with the result affects the speed performance of the system. AstraZeneca's recommendation is that they are held in the instrument database until the results are reviewed and approved and can then be discarded as this exactly simulates the current process when the plates are read by eye. Another challenge discussed was the validation as per the pharmacopeia chapters for alternative methods. Are there specific minimum expectations to define equivalent or better since there is subjectivity in counting by humans for this task? The company indicates that qualification versus the current process is more relevant as the method is not changing only the method for reading is being standardised.

4.3. AI for Chromatographic Peak Integration, Merck KGaA

Chromatography-based methods are widely used in quality testing and process control. However, the processing of chromatographic data was found inadequate in the past during GMP inspections, leading to the need for a robust technological solution. Merck KGaA has developed an AI-based solution using convolutional neural network (CNN) models for chromatography peak integration to address these challenges (Satwekar *et al* 2023). According to Merck KGaA, this technology offers benefits in compliance, efficiency, and supports Industry 4.0 objectives in real-time release testing, automated QC, process analytical technologies, and continuous manufacturing. Their approach is claimed to align with the draft EMA reflection paper on the use of AI in the medicinal product lifecycle demonstrating the use of representative data, rolling window cross validation approach (data organised as per calendar time) for model training, validation & testing, human in the loop, full GxP traceability with auditability, data, and model management with effective AI operational performance tracking metrics, and a risk-based based approach with exploratory unscripted testing (Computer Software Assurance, FDA draft). Furthermore, their prototype is a locked universal AI architecture having model generalisability and robustness to train/re-train models with almost no hyper parameter changes. The adaptability to new data, methods, and molecules is achieved through a no-code/algorithm change approach, offering human oversight, simplicity, consistency, stability, and robustness for widespread adoption. Some challenges and potential solutions identified by the speaker are as follows.

Explainability - black box models: CNN models often have non-linear and complex relationships, making it difficult to explain their decisions. To address this, Merck KGaA proposes a shift towards AI operational performance assurance (OPA). This approach involves rigorous evaluation and assurance of the AI system's operative effectiveness, aligning with GxP principles.

Data Evolution: AI models must adapt to evolving data to maintain their performance and relevance. The AI models should be trained on representative data, and constantly monitored for evolving data and the respective AI operative performance metrics. This leads to the embracing of a data driven dynamic validation approach of unscripted exploratory testing. It involves experience-based testing by spontaneous design and test based on evolving data and re-training the AI models for better performance across the lifecycle through Machine Learning Operations (MLOps). We emphasise the need for regulators to provide a clear, structured, and harmonised guidelines on this topic.

Regulatory expectations in submissions - AI black box models: There is a lack of clarity on the information needed to be reported in product submissions and on the information that should be part of the PQS.

Unpredictable evolution of data may necessitate frequent retraining of AI models. To address these challenges, a risk-based flexibility approach could be adopted, allowing for retraining of AI models as needed within the PQS. The use of universal locked validated architectures can support this approach. Regulators may consider defining classes of training/re-training models based on hyper-parameter tuning, as low change (minimum to no tuning), medium change (moderate tuning), and high change (significant and frequent tuning) and define clarity in guideline based on its fit for intended use and provide flexibility.

4.4. Visual Inspection Robot using Machine Learning Algorithms, Roche

The Roche presentation showed the planned application of machine learning algorithms in manufacturing on the example of the visual inspection robotic unit (VRU), a system for 100 % inspection of parenteral finished products. The VRU was developed for the use in small to mid-size batches. It features a series of robotic arms and 6 camera stations for flexibly handling product primary containers of varying type and shape, coupled with the possibility to use machine learning (deep neural networks) to train image analysis algorithms. These ML algorithms, which could be deployed based on need for the individual detection stations, are delivering improved detection of defects while minimising false positives, compared to conventional Automated Inspection Machines (AIM). The system has been developed by an established manufacturer of inspection systems jointly with Roche's Manufacturing Technology teams and is planned to be deployed in the next 1-2 years into drug product plants.

The main quality and GMP regulatory challenges identified concern 1) the categorisation of the change from conventional AIM, 2) required supporting documentation needed, 3) the principal approaches of qualifying the algorithms, also with the enhanced data governance for machine learning algorithms and model performance monitoring in mind. In the first mode of implementation - using a locked algorithm for 100% in-process inspection - Roche assesses the system as GMP and PQS-documentation relevant, but not subject to registration in the CTD. This is based on precedent of the documentation with existing both human operators as well as automated inspection schemes and the related documentation practices. The approach to a GMP-appropriate deployment of the system relies on a systematic approach to developing the algorithms, following the Roche Best Practice document for AI/ML models validation and lifecycle. In this case, the development is performed by the experts of the vendor of the equipment (human in the development loop). Roche then deploys the algorithm in their factory and qualifies the performance by utilising conventional test kits which have been analysed repeatedly by subject matter experts (human in the loop). The approach to a GMP environment around this technology is strongly adapted from existing ISPE and PDA best practice documents and white papers (for example "Applying Machine Learning to the Visual Inspection of Filled Injectable Drug", Products PDA Journal Oct 2023). In the future, the update of the Annex 11 to the EU GMP guidelines is

expected to bring clarity on the requirements for Computerised System Validation (CSV) of AI/ML system and data validation approaches.

4.5. Plenary discussion on Artificial Intelligence and Machine Learning

All presentations of the second day showed a practical implementation of AI/ML applications in the pharmaceutical industry, accompanied by considerations from the user side, offering the speakers the opportunity to present their challenges and proposed solutions.

Industry stressed that overly prescriptive guidelines related to AI and ML might present regulatory hurdles or even restrict early-stage development. They proposed using a risk-based approach offering the necessary flexibility and, at the same time, ensuring the required safety is met, especially in early stages of development. In addition, it was suggested that guidance should encourage the use of best practices and industry-applied standards, as these documents should both fill the gaps that could arise in guidance and allow flexibility in relation to the rapidly evolving field. The revision of EU GMP Annex 11 was highlighted by QIG; it will contain considerations towards AI and ML, which are expected to be sufficient to support implementation of AI/ML in GMP environment. No additional detailed GMP-guidelines might be required at this stage, as no blocking factors for implementing AI/ML were identified from the different cases presented. General concepts of current guidelines are still applicable.

Industry indicated that the EU AI Act regulation should reflect more the pharmaceutical applications and concerns with adapted risk levels. The EU AI Act is considered to be a possible limitation towards the implementation of AI/ML-based applications. This could not be addressed by EMA, as this is not an EMA document.

Regulators expressed concern about the use of AI/ML–based models without the knowledge of how to implement them appropriately and raised the question on whether changes in personnel (new roles, expertise) and validation and revalidation procedures for AI/ML-based applications are to be considered. Industry confirmed that changes between the traditional validation process and a new process adapted to the implementation of models are to be expected. The solution of involving data scientists and process experts in the validation processes was highlighted by industry. In the context of validation procedures, industry expressed concerns about the need to clearly define what information about a model (e.g., the exact algorithm, training data) needs to be included in the dossier and what information can be part of the PQS and how changes to the models should be handled. Industry emphasised that resources should be handled with care on both the regulators and industry sides. It was also highlighted by industry parties that GMP inspectors should not be overloaded by integrating everything in the PQS and assessors should not be overloaded either with variation submissions for every change to the model. As a proposed solution for GMP inspections, industry representatives suggested improving risk communication between operators and regulators by focusing on the functionality of the presented model/AI-ML-based application. This was considered reasonable by the regulators. Lifecycle management was mentioned by both industry and regulators as a crucial factor for the deployment of these models in practice. Industry suggested to consider keeping EU GMP Annex 11 as a living document to update guidance as experience evolves. Regulators indicated that a living Annex 11 document is not feasible. Therefore, the new Annex 11 will only consider principles for implementing AI in manufacturing. FDA referred to its guidance for near-infrared analysis methods, which describes an approach to change management that could also be applicable to AI/ML-based applications. A reporting category is proposed based on the impact of the model, the impact of the change on the model and the change management by the applicant.

The large amount of data that accumulates e.g. for optical systems and the need to store all the metadata was discussed. It was acknowledged that new technologies are accompanied with additional

and large amounts of digital data. Clarification on the requirements on data governance/storage for automated systems, compared to a manual process, was requested. Despite the fact that it might be feasible to store all the data, regulators explained that the need for data storage should be assessed depending on the use and criticality of the data.

The human-in-the-loop (HIL) concept as part of model performance monitoring/model control was raised by regulators, with a focus on the need and the role of the human. Industry emphasised the need for a human-in-the-loop (e.g., for the training of models) and depending on the maturity and confidence in the model, the balance between fully autonomous and HIL can be configured. Only for decision making AI-models there would be no HIL involvement. In all other cases HIL is considered. Following this discussion, industry stressed the importance of having defined terminology, also with a view to have clear and defined regulatory guidance.

Regulators stressed that even if AI-models are making decisions in certain aspects of quality control or manufacturing stages, the decisions on release of a batch have to be made by a human Qualified Person only supported by technology to fulfil legal responsibility of the duties laid down in Article 51 2001/83/EC.

4.6. General sum up on Artificial Intelligence and Machine Learning

The final session of day 2 summarised the main aspects discussed, including the challenges and proposed solutions on Artificial Intelligence and Machine Learning for GMP applications presented by stakeholders and the identified areas for follow-up. These are summarised in the tables below. Overall, as in day 1, there was general agreement by all parties that the development of dedicated guidance on models covering terminology, model criticality determination and data requirements, clarification of the regulator's expectations with regards to the boundaries between the dossier and the PQS, and focus on principles, concepts, and non-specific performance criteria, would be beneficial. QIG and FDA participants agreed to continue the dialogue in the area of modelling, AI/ML to jointly support stakeholders as much as possible.

Artificial Intelligence and Machine Learning
Challenge 5 The new technologies are accompanied with additional and large amounts of digital data. Clarification on the requirements on data governance/storage for automated systems, compared to a manual process, is requested. As an example, the large amount of data that accumulates e.g. for optical systems was described and the need to store all the metadata. **Proposed Solution** To discuss an overall strategy to define which data needs to be stored. **Areas for follow-up** Consider developing Q&A to define/clarify the requirements with regards to data storage. E.g., by rating the concerned data regarding their impact or whether they have an added value.

Artificial Intelligence and Machine Learning

Challenge 6

AI discussions rely on self-defined terminology. No accepted harmonised standards are currently available bridging IT terminology and GMP terminology.

Proposed Solution

As in day 1, the desire to have, ideally, globally aligned terminology on e.g. definition of AI, machine learning, deep learning, supervised and unsupervised learning, verification and validation of algorithms was reported.

Areas for follow-up

Continue progress in the field and assess pre-existing norms and the EU AI act. Maintain dialogue with US FDA and other regulators.

Challenge 7

To address the boundaries between integration into the Pharmaceutical Quality System (PQS) and the dossier, and the expectations with regards to the level of description and also the level of explainability without overregulating. This is also part of challenge 1 from day 1.

Proposed Solution

Evaluate the risks of the models in pharma applications and provide some clarifications in guidance on risk considerations, classification of models and expectations for the dossier, including lifecycle management.

Areas for follow-up

Develop guidance on modelling (see challenge 1 from day 1).

Monitor progress to collect information for future EU GMP Annex 11 revision focusing guidance on principles and not on prescribed performance criteria as it is a rapidly evolving field.

Challenge 8

The terminology of human in the loop (HIL) is identified as new and is not addressed in current GMP-guidelines. In addition, depending on the level of knowledge and the understanding of the models, new roles of personnel might be needed.

Proposed Solution

To evaluate the need of HIL in relation to the type of the model and the type of the application.

Areas for follow-up

Consider future guidance to clarify expectations with regard to monitoring of models by HIL.

Challenge 9

Lack of certainty on whether AI/ML may be accepted by regulators.

Missing guidance on the requirements for algorithms information in the dossier and their lifecycle management hinders their implementation. Guidance is to focus on principles, not on performance

criteria of this rapidly evolving technology. Performance criteria often need to be continuously reassessed and adjusted as per the evolution of data. Otherwise, strict requirements might hamper progress.

Proposed Solution:

To define requirements for low, medium and high impact AI applications.

Some participants suggested that only high impact applications were to be described in the dossier. The information needed in the dossier should be defined. Dynamic CTD might be implemented, that reflects the lifecycle of algorithms.

On the other hand, it was suggested that low/medium impact applications could mainly be handled within the PQS and assessed during GMP inspections. PQS processes for lifecycle management of algorithms need to be defined.

Areas for follow-up

Monitor progress in the field and define risk-based criteria for algorithms based on, for example, type of algorithm, application, impact to product quality and patient safety, and detectability of failure. Tailor depth of assessment and surveillance strategy based on categorisation.

Assess whether there is a need for implementation of new or adaptation of existing guidelines for quality assessors and GMP inspectors.

5. Next steps

The LLFG meeting provided a good forum to gather information from our industry and academia stakeholders on the challenges they face and anticipate on the application of digital novel technologies, and their proposed solutions to overcome those.

The QIG will use the information gathered to inform its future discussions and consider which additional actions are necessary to facilitate the implementation of these technologies. These will include further follow-up discussions with stakeholders and international partners, when appropriate.

Following the informative and transparent discussions at LLFG, the intent of the QIG is to draft relevant guidance, focusing on principles, in order to support stakeholders on their developments and implementing of process models/AI/ML in manufacturing. The retained, and acknowledged message, is flexibility, no over-prescription.

The different case studies presented highlighted the importance of a clear identification of the context of use of a model as a prerequisite for any model development; all subsequent considerations, including model risk, should flow from this key starting point.

The upcoming guidance shall focus on the suitability of the model for the intended use as an essential part of model validation, under the overarching role of process validation. The approach for validation is not a one-size-fits-all, and whatever the proposed strategy to demonstrate that a model is fit-for-purpose and the process under state of control, it should always follow risk in the context of use. It is recognised that there can be limitations to the model use in the first phases of development and implementation, but this can be explained to the Authorities with a supporting risk assessment.

Since data and models are aimed to evolve by nature, regulators acknowledge the need for a more agile framework for change control. Practical deployment of models and their lifecycle will be a central point of the future guidance.

Whereas these joint LLFG meetings are considered of high value to have open discussions with all stakeholders and share information, the QIG invites individual organizations that want to discuss confidential details with the QIG to apply for a 1:1 meeting with the QIG (early discussion) or apply for scientific advice requesting QIG involvement (written feedback). For details on how to get in touch with the QIG, please consult its webpage.