ICH REFLECTION PAPER

Proposed ICH Guideline Work to Facilitate the Adoption of Advanced Pharmaceutical Manufacturing

This paper identifies key areas where globally harmonised regulatory guidelines could facilitate the adoption and regulation of advanced manufacturing technologies to improve pharmaceutical development and manufacturing. There are opportunities to address advanced manufacturing technologies in new and existing ICH guidelines. Clear and harmonised expectations on advanced manufacturing technologies help the development, implementation and regulatory assessment of these technologies. Examples of advanced manufacturing technologies are process modelling, including artificial intelligence (AI)-based models, and decentralised or distributed manufacturing. Through external engagements, international manufacturers have noted the lack of global regulatory alignment as one reason for not pursuing and adopting these and other advanced manufacturing technologies.[1] New issues arising from novel manufacturing paradigms require re-examination and alignment of existing policies and practices, and provision of new or revised guidelines for manufacturers and regulators. Ideally, ICH guidelines with globally harmonised regulatory expectations would enable the implementation of agile and flexible networks of manufacturing in different regions and areas.

A. Background

Advanced pharmaceutical manufacturing technologies have the potential to improve pharmaceutical quality, provide greater flexibility and agility to the manufacturing process, and enable more timely response to urgent health issues. The global pandemic has underscored the need for agility and flexibility in the manufacturing process to maintain a robust supply chain while ensuring pharmaceutical quality. Advanced manufacturing technologies can bring advantages such as rapid pharmaceutical development, mitigation of supply chain disruptions that can lead to shortages, and efficient change management that could lead to more efficient regulatory oversight for maintaining the availability of drugs. Continuous manufacturing technology, for example, can increase or decrease production output rapidly with no change to equipment size or facility, and it can also provide greater assurance of product quality through

[1] E.g., ISPE *Enabling Pharmaceutical Innovation: Delivering for Patients* (2024, April 25).

enhanced control and real-time measurements. Further, continuous manufacturing provides the opportunity to accelerate new approaches for process development and process monitoring.

The recently implemented ICH Q13 guideline is intended to facilitate international harmonisation and reduce barriers to adopting continuous manufacturing for biological and chemical drug substances and drug products. This guideline explains scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing and builds on existing ICH Quality guidelines. However, there are innovative areas beyond the scope of ICH Q13 that require the development of new ICH guidelines or updates to existing ICH guidelines.

There are potential benefits to advanced manufacturing technologies, but there is generally a lack of consistent technical risk frameworks and regulatory standards for development, implementation, and regulatory assessment of these technologies. Manufacturers and regulators should work together, as appropriate, to ensure that manufacturing processes are adequately designed and controlled with appropriate control strategies based on risk considerations of the product and process.

There is an opportunity to advance global alignment on scientific and regulatory expectations early in the lifespan of new manufacturing technologies that can be critical to their successful uptake. The goal of this paper is to identify potential areas for long-term harmonisation of global policies and scientific and technical requirements for advanced manufacturing technologies. External factors, such as regional policies and sufficiency of regulatory experience, may influence the timeline for addressing new topics and developing future guidelines through a stepwise approach. This paper addresses three key advanced manufacturing topics for potential successive future harmonisation: process modelling, continuous process verification and decentralised or distributed manufacturing.

Process Modelling

A model is a simplified representation of a system using mathematical terms.[2] Models can be used to enhance scientific understanding of a system, predict the behaviour of a system under a set of conditions or facilitate advanced control strategies through real-time data exchange between the model and the physical system. Models can be applied to every stage of

[2] ICH Quality Implementation Working Group Points to Consider (R2): ICH-Endorsed Guide for Q8/Q9/Q10 Implementation (December 2011) and ICH guidance for industry Q8, Q9, & Q10 Questions and Answers: Appendix Q&As from Training Sessions (July 2012).

pharmaceutical development and manufacturing.[3] The enhanced scientific understanding from models can be used to accelerate pharmaceutical development and support the manufacturing of high-quality drugs. ICH M15 provides recommendations for model-informed drug development while ICH Q2 and ICH Q14 provide recommendations for the development and validation of multivariate calibration models associated with analytical procedures.

The use cases of models within pharmaceutical manufacturing extend beyond drug development and multivariate calibration models. Process models might be considered digital representations of physical pharmaceutical manufacturing processes. Such models are increasingly being used to accelerate and improve process design, scale-up, site transfer, process monitoring, and process control. Process models can be used with both conventional manufacturing and advanced manufacturing approaches, such as continuous manufacturing and decentralised or distributed manufacturing. Additionally, process models can become a critical element of the control strategy to ensure consistent product quality.

The appropriate type of model can depend on the existing knowledge of the physical system, the data available or able to be generated, and the objective or intended use of model. The ICH Quality Implementation Working Group (QIWG) *Points to Consider* established the principle that a model's impact (i.e., the model's contribution to assuring product quality) guides the extent of regulatory oversight. However, there is currently a need for global harmonisation on multiple aspects (e.g., terminology, model risk framework, basis for regulatory oversight, and data requirements) to support the use of models in pharmaceutical manufacturing.

Another global challenge for modelling is using an effective model validation framework to establish that the model is fit for purpose for its intended use or application over the product lifecycle. Different model validation approaches may be appropriate considering the different types, uses, and risks of models. Manufacturers require regulatory guidance to understand how these differences impact the expected level of model validation and model maintenance activities over the product lifecycle. Additionally, manufacturers require guidance on regulatory notification of model updates considering model risk and maturity of a site's quality system. The ICH *QIWG Points to Consider* does not address the scientific and regulatory considerations for linking model risk to model validation and lifecycle management activities. The absence of a harmonised regulatory framework for process model development, implementation, continual improvement, and change management can deter the implementation of process models across regions. New types of AI models might further challenge the regulatory frameworks for process

[3] See ICH Q13 guideline: Continuous Manufacturing of Drug Substances and Drug Products, Section 3.1.7. for examples of process models applications in continuous manufacturing (March 2023).

models. Accordingly, regulators are actively developing regional guidelines to address the rapid advancement of digital technologies and AI in pharmaceutical manufacturing.[4,5]

As regulators gain experience with AI models, a new ICH guideline on process models could provide a comprehensive framework with principles that might be applicable to AI models, recognizing that the ICH *QIWG Points to Consider* did not explicitly foresee these new types of AI models. Given the potential for increased use of models in pharmaceutical manufacturing, there is a need for ICH guidelines to provide harmonised regulatory and technical considerations for the development, validation, implementation, and maintenance of process models.

Continuous Process Verification

Manufacturing process validation is the collection and evaluation of data which establishes scientific evidence that a process is capable of consistently delivering quality product throughout the product lifecycle.[6] Further, process validation is documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.[7]

Validation of manufacturing processes can be achieved in different ways. The traditional process validation approach typically uses data from a fixed number of batches manufactured prior to marketing pharmaceutical product, in addition to other information. Processes may also be validated using a continuous process verification approach as defined in ICH Q8(R2), or a hybrid approach which combines elements of traditional process validation with continuous process verification.[8]

ICH Q8(R2) defines continuous process verification as an alternative to traditional process validation in which the performance of the manufacturing process is continuously monitored and evaluated. Unlike the traditional "fixed number of batches" approach, continuous process verification leverages data from every batch manufactured on an ongoing basis to monitor process performance and is enabled by product and process knowledge and advanced process monitoring and control strategies. Continuous process verification may be used to validate processes employing both conventional and advanced manufacturing technologies. Continuous

[4] Stakeholders' Consultation on EudraLex Volume 4 - Good Manufacturing Practice Guidelines: Chapter 4, Annex 11 and New Annex 22 - European Commission
[5] FDA draft guidance for industry *Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products* (January 2025).
[6] FDA guidance for industry *Process Validation: General Principles and Practices* (January 2011).
[7] EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions (November 2016).
[8] ICH guidance for industry Q8(R2): *Pharmaceutical Development* (August 2009).

process verification is well-suited for processes with enhanced process monitoring and control strategies that facilitate ongoing monitoring of process performance, such as continuous manufacturing.

The benefits of implementing continuous process verification extend beyond meeting regulatory requirements for process validation for a new technology. For example, analysis of extensive data from every batch, including in real time, can help identify sources of variability and risk, permit pre-emptive corrective and preventive actions, continually improve the process control strategy, and increase process knowledge throughout the product lifecycle. Adoption of continuous process verification will enhance process understanding, process robustness and product quality.

Although continuous process verification is briefly addressed in the ICH *QIWG Points to Consider* and represents an advanced approach to process validation, it has not been widely adopted. There is a need for further clarification on the expected level of product and process understanding, process monitoring and control strategy, and the information and data needed in the dossier to support continuous process verification. Additionally, traditional process validation approaches may not be well-suited for advanced manufacturing technologies and could potentially deter their implementation. Global harmonisation on regulatory expectations and clarity on implementation strategy would signal the global adoption of continuous process verification, as well as encourage other related advanced manufacturing approaches such as decentralised or distributed manufacturing.

Decentralised or Distributed Manufacturing

Decentralised or distributed manufacturing might be considered a manufacturing paradigm in which pharmaceutical manufacturing of a drug substance, intermediate and/or drug product is decentralised or distributed across multiple manufacturing sites in multiple locations. Typically, the networked sites produce smaller product volumes using decentralised 'remote' manufacturing units, linked through a central 'hub' location and could involve a higher degree of automation and process monitoring. In contrast, conventional manufacturing produces large product volumes in a few facilities or single facility. Decentralised or distributed manufacturing when combined with process monitoring based on models can provide real-time data exchange between multiple manufacturing locations. This data exchange can enable the observation and anticipation of system behaviours to rectify anticipated adverse outcomes before they occur. Decentralised or distributed manufacturing can be combined with continuous process verification and modelling approaches described above. The reciprocal data flow obtained can be used to inform whether the networked system is functioning as intended and is operating under a state of control to ensure the quality of products.

As manufacturers explore novel manufacturing paradigms, such as decentralised or distributed manufacturing and the use of process models for process control across manufacturing sites, they may require regulatory guidance related to new issues. In distributed or decentralised manufacturing, for example, all components of the pharmaceutical quality system (PQS) might not be located at each manufacturing site in the network. Instead, many of the PQS functions for each site might be centralised within one location. Similarly, a process model used in the process control strategy might not be accessed at the same physical location as the site conducting the manufacturing unit operations. Manufacturers need guidance on multiple PQS issues, for example, roles and responsibilities for manufacturing and product quality functions, and remote oversight of facility, equipment, materials, components, and manufacturing activities.

The production of small product volumes at multiple locations raises several other issues, such as those related to considerations for consistency and comparability of product quality among different locations, product release, stability testing, and process validation. For example, traditional approaches relying on physical sampling and off-line testing of material or removal of a large quantity of samples for stability testing may no longer be appropriate or feasible when small quantities of material are made at multiple sites. The incorporation of alternative monitoring tools in the control strategy (such as process analytical tools/models) may help mitigate risks by providing real-time or predictive information about product quality and process performance. Current expectations for testing critical quality attributes for product release or in-process testing (e.g., via direct interrogation of material) may be challenged by newer technologies.

A potential future effort to align globally harmonised expectations and general principles for decentralised or distributed manufacturing might eventually be considered, dependent on further technology development and regional legislation or policy developments. The timing and scope of this potential initiative might also be informed by stakeholder input and evolving regulatory expectations, aiming to support the development of robust control strategies that effectively minimise risks and enhance product quality assurance.

B. Enabling the Use of Advanced Manufacturing Technologies

This reflection paper identifies a series of pharmaceutical development and regulatory decision-relevant subjects that may arise during advanced manufacturing technology implementation and subsequent lifecycle management. There is potential for ICH guidelines to outline methods and standards to be applied when preparing regulatory submissions with advanced manufacturing technologies. To address the needs of manufacturers, there may be opportunities to update existing ICH guidelines and/or develop new ICH guidelines. For example, there are existing ICH

guidelines and associated materials that address modelling in a general manner. The ICH Q13 guideline and associated training materials have content on process models that could be incorporated into the development of a global regulatory framework for process modelling.[9, 10]

The *ICH QIWG Points to Consider* also includes a modelling section. The approach to modelling described therein, particularly lifecycle management and impact categorisation, mainly considered multivariate calibration models for analytical procedures based on the knowledge and experience available during the development of that ICH document. The approach described in the *ICH QIWG Points to Consider* may not be best suited for AI models used as part of a dynamic control strategy and in continuous manufacturing. Regulators and industry are recognizing the need for a modern risk-based classification of models and lifecycle management approach considering the different types and risks of process models. AI or continuous learning models, for instance, can pose a significant challenge for regulators as post-approval model verification activities need to be balanced with the ongoing changes to the model as new information is generated.[11]

ICH guidelines can harmonise standards and best practices for lifecycle management of process models and can be developed by building on concepts in existing guidance. For example, EMA's *Preliminary Considerations on Pharmaceutical Process Models* guidance[12] addresses general principles for process models that reflect the use of performance-based approaches in modelling pharmaceutical manufacturing processes. Other medical product fields, such as medical devices, have adopted principles that provide detailed recommendations on model validation. For example, the ASME V&V 40 technical standard *Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices*, which was recognised by FDA's Center for Devices and Radiological Health (CDRH) for medical devices,[13] articulates risk principles that might be applied to other domains. Applicable verification and validation principles and content from appropriate sources can be leveraged to establish a harmonised approach for process models used in pharmaceutical manufacturing.

[9] ICH Q13 guideline: Continuous Manufacturing of Drug Substances and Drug Products (March 2023).
[10] ICH Q13 IWG Training on Continuous Manufacturing of Drug Substances and Drug Products (2023).
[11] O'Connor, et al., An examination of process models and model risk frameworks for pharmaceutical manufacturing, International Journal of Pharmaceutics: X, Volume 8, 2024, 100274, ISSN 2590-1567, https://doi.org/10.1016/j.ijpx.2024.100274.
[12] EMA Preliminary QIG Considerations regarding Pharmaceutical Process Models. Quality Innovation Group. European Medicines Agency (europa.eu). (2024, February 22).
[13] For more information visit CDRH's guidance for industry *Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions* (November 2023).

While not primarily focused on advanced manufacturing technologies, some existing ICH guidelines may address aspects relevant to regulatory submissions that use advanced manufacturing technologies. For example, the revision of ICH M4Q(R1) (ICH M4Q(R2)) intends to capture quality information needed to support registration and to specify the location in the application for submission of lifecycle management elements. The revision intends to facilitate submission of information supporting emerging concepts such as advanced manufacturing, digitalisation, data management, process models, and advanced analytical tools. The ICH Q10 and Q12 guidelines provide a conceptual framework to facilitate the management of post-approval changes in a more predictable and efficient manner. This framework helps to promote continual process improvement and innovation throughout the product lifecycle and can also be applied to advanced manufacturing processes. For example, it may help to streamline post-approval model-related changes or updates by considering the applicant's intended use of models in the context of product, process and control strategy development.

Public engagements over the past several years[14] have identified questions that could be addressed to inform technology development and implementation. The questions provided below are not exhaustive but rather convey a range of opportunities to inform development and decision-making.

Process Modelling

- What are the expectations for in-process material testing and release testing of product when a model is employed for process control?
- What are the expectations for risk-based validation of pharmaceutical manufacturing models?
- What are the expectations for a lifecycle maintenance approach of a model over its lifespan, especially for frequently updating process models (e.g., AI models that learn and self-adjust)?

Continuous Process Verification

- How can traditional and continuous process verification approaches be employed for the initial and ongoing manufacture of pharmaceuticals using advanced technologies?
- Can regional regulatory approaches to continuous process verification be aligned?

[14] FDA engaged stakeholders on advanced manufacturing in four different forums: i) discussion paper Distributed Manufacturing and Point-of-Care Manufacturing of Drugs (October 2022) for public comment in the Federal Register (Docket No. FDA-2022-N-2316) ii) Workshop on Regulatory Framework for Distributed and Point-of-Care Pharmaceutical Manufacturing (November 2022) iii) a discussion paper Artificial Intelligence in Drug Manufacturing (March 2023) for public comment in the Federal Register (Docket No. FDA-2023-N-0487), and iv) Workshop on the Regulatory Framework for the Utilization of Artificial Intelligence in Pharmaceutical Manufacturing (September 2023).

Decentralised or Distributed Manufacturing

- How should decentralised or distributed manufacturing be defined and what are the PQS expectations when all components of the PQS are not located at each physical location?
- What are the expectations for the PQS and product release when all manufacturing units are not located at the same physical location?
- Are there unique regulatory considerations for smaller manufacturing units producing smaller product volumes at multiple locations (e.g., stability testing, qualification of utilities and equipment, process qualification)?

C. Topic Sequencing, Timing and Other Considerations

A phased, stepwise approach to guideline development in this area will be needed (e.g., three separate guidelines) as it will not be feasible to address all topics simultaneously. Each guideline would address distinct topic areas, reflecting the differing knowledge requirements across the field. The development of any new guideline would begin with a new topic proposal. Topic prioritisation will be informed by regulatory experience and scientific knowledge. However, timing to initiate this effort may be influenced by external factors, including regional legislation or policy development. Additional input from stakeholders on their development and implementation of advanced manufacturing technologies will help inform and shape future guideline development in this important area.

A new ICH guideline on process models that could facilitate a framework and broader technology adoption to accelerate pharmaceutical development and manufacturing would be a preferred first step in this effort. The maturity of alignment and collaboration among global regulators support the development of a new guideline for process models as the next step. Such a guideline would clarify the *Points to Consider* document regarding the regulatory expectations related to the implementation and use of process models, including documentation required in dossiers related to models and model updates over the lifecycle. This work would also include revising *Points to Consider* based on scientific and regulatory considerations for linking model risk to intended use and decision consequence.

These quality topics should build upon one another for efficient implementation. Since process models could potentially be a component of control strategy of a decentralised or distributed manufacturing process, a new process models guideline could be leveraged by other future potential topics, i.e., continuous process verification and decentralised or distributed manufacturing. Such a guideline can facilitate the implementation of process models for data-rich analysis of process parameters and input material attributes. Data contributes to process

performance and product quality and addresses the scientific and regulatory considerations on linking model risk to model validation and lifecycle management activities.

Following the development of an ICH guideline for process models and revision of *Points to Consider*, it is proposed to address continuous process verification. Large meaningful data from process models can be leveraged into data packages to support continuous process verification. Continuous process verification can enable a manufacturer to monitor and adjust the process and/or control strategy, as appropriate over its lifecycle, to foster continual improvement and enhance productivity.

A potential subsequent guideline for decentralised or distributed manufacturing could reference and build upon the applied principles established for process models and continuous process verification. A guideline for decentralised or distributed manufacturing might enable the use of models for quality decision-making for product release at multiple geographical locations validated though continuous process verification.

Existing regulatory guidance, ongoing collaborative international efforts, past public engagements, and a large body of technical literature could support the development of proposed guidelines on advanced manufacturing topics. Interested parties seeking advice on specific advanced manufacturing questions can interact with regulators through specific avenues, including FDA, United States' Framework for Regulatory Advanced Manufacturing Evaluation (or FRAME) initiative, the Emerging Technology Program (or ETP), and the CBER Advanced Technologies Team (or CATT); the European Medicines Agency's Quality Innovation Group (QIG); the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) Consultation; and Japan's Pharmaceuticals and Medical Devices Agency Innovative Manufacturing Technology Team (IMTT).

FRAME focuses on policy elements and regulatory expectations with a goal to establish a regulatory framework that provides clarity and reduces uncertainty for products manufactured using advanced manufacturing technologies. The ETP and CATT focus on supporting potential applicants by providing opportunities for early discussion of technical and regulatory issues associated with the implementation of advanced manufacturing technologies. Additionally, the ETP coordinates the regulatory assessment and inspection associated with applications incorporating such technologies. MHRA Consultation was developed to create a new framework to enable the supply and increase the availability of innovative new medicinal products to patients. Similarly, the QIG was set up to support the development and registration of innovative technologies and products, by clarifying the regulatory requirements for manufacturing and control early on for interested parties. IMTT was established to discuss regulatory issues related

to quality assessment and GMP inspections to facilitate the introduction of innovative manufacturing technologies, primarily continuous manufacturing, while ensuring appropriate quality.

While multiple regulatory agencies have established programs for advanced manufacturing technologies that have garnered interest from industry, the lack of harmonisation across these initiatives may discourage manufacturers from pursuing such technologies despite the potential to significantly enhance product quality. Therefore, the development of guidelines on these topics should include various regulators. ICH endorsement of this reflection paper can lead to harmonisation of potential future work on these proposed topics or others that may be identified by the ICH Management Committee or ICH Assembly. There is a global desire for harmonisation on regulatory expectations in advanced manufacturing and ICH should consider these topics during the annual ICH new topic selection process.