26 March 2024

ISPE appreciates the efforts from the EMA QIG to advance the "Preliminary QIG Considerations regarding Pharmaceutical Process Models." This document is a significant step and clearly outlines some of EMA's current thinking on topics that have been raised by industry in forums such as the 2023 QIG Digital Listen and Learn. In particular, clarification provided on the QIG's thoughts on the extent to which registration of process model algorithms is necessary, assessment of model risk against scope of use, and model maintenance in terms of registration vs. management in PQS is helpful. ISPE has several recommendations to further assist the QIG in updates to the current document, or for the development of future guidance to industry.

1.) Terminology and Definitions

Certain terminology used throughout the document is either new or undefined. Many of these terms are consistent with related guidances or standards that are not directly applicable to pharmaceutical manufacturing (e.g., ASME Validation & Verification (V&V) 40, FDA CDRH's "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions"). ISPE appreciates the EMA QIG's attempt to consolidate the considerations of these important sources into the current position; however, some terms are either not currently defined under ICH or other existing guidance or can create confusion when taken together with the terms outlined under the ICH Q8/9/10 Points to Consider Questions and Answers (PtC Q&A) document.

For example, the current use of "model risk" as the fundamental basis for model classification does not directly align with the definition of "model impact" under ICH Q8/9/10 PtC Q&A. Given that the ICH guideline is the fundamental basis by which industry currently evaluates the regulatory impact of process models, the revised terminology without further clarity of its relationship to the ICH terminology is problematic. Therefore, until the linkage with ICH terminology can be better defined, the QIG should rely primarily on the ICH terminology and in particular the evaluation of model impact.

In addition to model risk, ISPE also recommends providing definitions or clarity for the following terms used throughout the document:

- Adaptability
- Model risk
- Model adequacy
- Model maturity
- Digital twin
- Digital shadow
- Comparator
- Model maturity
- Model adequacy (FDA credibility)

The specific definitions for these terms will have a considerable impact on some of the associated scope of related activities (e.g., for digital twin, the degree of ongoing life cycle management will depend on the scope of the precise definition). ISPE also recommends reiterating the ICH definitions of "model impact" in the defined terms.

2.) Assessment of Model Risk (Impact)

As mentioned under Item 1, ISPE recommends the use of "model impact" in lieu of the term "model risk." There are several areas in the existing EMA QIG position that may benefit from additional clarification against the current ICH Points to Consider (PtC) Q&A guidance.

For example, under line 57-59, the QIG refers to "risk to product quality"; while this can be understood in a general fashion, the ICH PtC Q&A does not specifically reference "risk to product quality" but rather "risk associated with the use of the specific model" and potential *impact* to product quality.

Under lines 63-65, some higher-level classifications are provided for process models, the implication being that they are representative of increasing degrees of model impact. To further expand on this, ISPE recommends any future guidance includes case studies that explore the process of determining model impact in context of the product, process, and control strategy.

Lines 75-77 present the concept of assessing model risk *in isolation*. While certain criteria may factor into the overall advantage of using one particular model for a given application, the overall risk or *impact* of such selection is entirely predicated on the context of use. Therefore, while EMA QIG may find some information regarding the basis by which a given model is selected helpful, generally this would be of limited value as part of a regulatory dossier and the true emphasis should be on the assessment of impact under the context of use. As such, this stipulation to carry out model risk assessment in isolation should be removed.

Further clarification in the future regarding the EMA QIG's perspective on the assessment of model impact in context of use is welcome, particularly for medium-impact models. Process development models should be fundamentally considered low impact, due to the limited scope of use and ultimate requirement to validate the final manufacturing process. It would be particularly important for EMA QIG to point out exceptions to this rule (e.g., lines 163-168 currently can be interpreted in several ways and may lead to model impact assignment that is different from the current thinking of the QIG).

3.) Model Performance, Registration Elements, GMP, and Life-Cycle Management

ISPE appreciates the EMA QIG's focus on performance-based approaches for process models, which is in line with the industry understanding and focus, in particular for process control models. In the future, further reference to and emphasis on the provisions of ICH Q12 would be welcome. While model performance is highlighted in the current document, it would be beneficial to place further emphasis on model performance as a consequence of its context of use. Likewise, the reiteration of fit-for-purpose validation is important, given that ICH Q8/9/10 PtC Q&A currently only stipulates that validation for low or medium-impact models should be considered on a case-by-case basis.

Some elements of model registration in the dossier may be misleading in the current version of the document. For example, lines 104-105 may be read to indicate that *all* low-risk models should be summarized in the dossier. This is not the current industry practice, and ISPE recommends that the QIG emphasize that inclusion of low-impact model information should be *optional* and primarily based on the applicant's *use of model-based conclusions in the dossier*. Line 107 indicates that the "choice of model" should be justified for medium-risk models. As mentioned previously, justification of a particular

model selection should not be necessary so long as the applicant can provide sufficient evidence of model performance (e.g., precision, accuracy) under the context of use for the proposed context of use. In some instances, it may be challenging to describe certain models under the dossier where elements such as predictive capability are not applicable (e.g., optimization algorithms). Further dialogue with the EMA QIG will be necessary to understand the expectations for the description of such models (e.g., is it possible to describe a number of discrete models in a single description and assign an overall impact level).

Consistent with ICH terminology, ISPE recommends revision of the statement in Line 121 of "subject to GMP only" to read "would be subject to management within the PQS, as appropriate." ISPE welcomes further dialogue with the EMA QIG on the criteria by which models would be required to be managed under cGMPs, as this is an important topic and industry is concerned that it could complicate inspection outcomes if industry and regulators are not aligned (e.g., cases where model details are updated and therefore are different from some aspects of the regulatory dossier, but still within the specified model scope and meet performance requirements).

Several elements of the proposed lifecycle management framework would also benefit from additional clarification. The EMA QIG's description of a "model maintenance protocol" is appreciated and is expected to be beneficial, although specific elements of the proposed protocol approach warrant further dialogue. Indeed, while the general application of this tool will be beneficial for the majority of cases, it is recommended to specify that the model maintenance protocol is optional, offering flexibility to use alternative approaches, as justified, since it is difficult to anticipate every process model use case prospectively. In addition, the need for ongoing lifecycle management should ultimately be tied to the context of use. As such, specific elements of the protocol that is filed in a regulatory dossier may need to be negotiated in the context of the particular model, its application, and the product in question. Thus, while the majority of medium/high impact models are expected to have more extensive and longer-term life-cycle management requirements, there may be cases where the specific context of use may shorten or limit these activities considerations should be provided for this aspect. Over time and continued model use and refinement, these activities could become less valuable and should be appropriately limited (e.g. from continuous to periodic verification).

4.) Other Recommendations

Several other recommendations for the EMA QIG are highlighted below that are outside of the broader comments above:

- A discussion of product development stage-appropriate expectations for models would be valuable, particularly for high-impact process models. This overlaps with the discussion of GMP considerations raised above as well.
- While the three general model classes are highlighted and discussed, ISPE would welcome further clarity on underlying principles of class-specific elements and expected dossier information, in particular for medium and high-impact models and for model performance.
- While the EMA QIG has indicated that large data sets would not be expected for registration, in cases where it may become necessary, use of an appropriate master file approach (e.g., platform

technology master files, should they be advanced under the current revision of the EU Pharmaceutical Legislation) is recommended.

- A broader discussion of the use of prior knowledge (e.g., beyond literature references) and acceptable approaches/limitations for model development, submission, and lifecycle management would be beneficial.
- The current document does not address considerations for use of models for in silico process characterization (e.g., synthetic datasets to supplement traditional process validation data). ISPE welcomes further clarification on the EMA QIG's position here.

ISPE is committed to continuing to work with EMA QIG on this important topic and we look forward to future opportunities to collaborate in forums such as the forthcoming EMA QIG Listen and Learn on process models this June.

Respectfully,
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cc: Scott Billman, ISPE Board Chair