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European Medicines Agency

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Submitted via email: ich@ema.europa.eu

Reference Number: EMA/CHMP/ICH/178042/2025

Subject: Comments on *ICH M4Q(R2) Guideline on the Common Technical Document for the registration of pharmaceuticals for human use: Quality*

Dear Esteemed Representatives of the European Medicines Agency,

We respectfully submit the following comments for your kind consideration and would be grateful if you would review them as part of the ongoing consultation on the Common Technical Document for the Registration of Pharmaceuticals for Human Use: ICH M4Q(R2).

ISPE wishes to express its appreciation to the EMA for providing the opportunity to comment on the draft guideline. We also recognize the positive intention of the guideline, which emphasizes critical elements of the dossier and aims to streamline lifecycle requirements.

The draft guideline represents a significant revision in how submissions are currently prepared, presenting notable implementation challenges. While this aspect is typically addressed by the ICH IWG, the considerable impact on both health authorities and industry compels us to highlight these issues early to support effective mitigation strategies. It should be noted that health authorities have extended periods of time for adoption of eCTD 4.0, and some still require paper copies; therefore, it is improbable that these authorities possess the resources, infrastructure, or funding necessary to update their systems promptly. This situation risks widening the gap between developed and developing regions, potentially leading to extended implementation timelines and requiring industry to submit documentation in both formats. The resulting administrative burden may discourage submissions to certain markets, further increasing disparity and undermining harmonization efforts.

Additionally, as the EMA serves as a pivotal reference authority for reliance mechanisms, clarification is needed regarding procedures when submission formats differ significantly. Considering these concerns, we recommend an extended and coordinated implementation period for new registrations and more clarity on how the revised guideline will apply to post-approval submissions to facilitate a phased adoption of the guideline.

Although the guideline does not explicitly intend this, there are cases where its scope has expanded, particularly with the application of biologics requirements to small molecules (e.g., line 267, starting

material suppliers are not required for small molecules). Device regulations also show an increase in scope due to varying review systems across regions (e.g., line 521, where providing a certificate of evidence for separate device registration is not required, followed by a risk classification). Additionally, there are instances of repeated information in both M.2.3 and M.3.3, such as detailed descriptions of manufacturing processes and the need for development data in both locations. This redundancy is inconsistent with the guideline's objective to differentiate life-cycle elements in M.2.3 from supporting material in M.3.3, rather than having similar content in both modules.

We trust that our comments will be taken into consideration and look forward to continued collaboration in shaping effective and pragmatic regulatory guidelines.

We appreciate the opportunity to contribute to this important consultation and remain committed to supporting the harmonization of global regulatory expectations. Please do not hesitate to contact us should you require any clarification or additional information regarding our comments.

Respectfully,

(Signature retracted for online publication)