Docket Number FDA–2021–D–0166; International Council for Harmonisation Q12: Implementation Considerations for Food and Drug Administration-Regulated Products; Draft Guidance for Industry

Comments from: International Society for Pharmaceutical Engineering (ISPE)

GENERAL COMMENTS ON THE DOCUMENT
ISPE appreciates the opportunity to review this important document which provides practical ICH Q12 implementation guidance for industry. The document clarifies the overall framework for categorization of post-approval changes to align ICH Q12 and FDA terminology, discusses the implementation of Established Conditions (ECs) including lifecycle and filing considerations, PACMPs and PLCM documents, as well as key considerations for PQS and Change Management. It is very helpful that the application of ICH Q12 to combination products is addressed in a comprehensive fashion, with specific examples provided to better illustrate the key concepts. ISPE would like to make the following recommendations: • That FDA revise the relevant CFR chapters and FDA post-approval change guidelines to align with the post-approval notification classification framework in the current document to indicate that CBE-0 is applicable for "minimal impact" changes. Based upon the current regulations under 21 CFR 314.70 and 21 CFR 601.12, as well as the existing FDA guidelines for post-approval changes (e.g., "CMC Changes to an Approved Application: Certain Biological Products", June 2021), CBE-0 supplements are intended for "moderate impact" level changes, and only annual reports are intended for "minimal impact" changes. • That proposed post approval reporting categories are not included in Module 3. For a sponsor, it is expected that Module 3 of CTD is a global document and regional specific proposals such as proposed regional reporting categories are included in region specific documents (i.e., 3.2.R section). • To remove the entire Section 7 "Maintenance of the Application". Up-to-date analytical procedures should be maintained at manufacturing sites and be made available during site inspections. There should be no requirement to submit them in an annual report (unless the changes impact ECs). The expectation to submit analytical procedures in Annual Reports essentially makes all analytical procedure parameters ECs, which is not the intended outcome of ICH Q12. The following pages contain specific comments on the draft guideline.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
60-61	"Notification moderate means a changes being effected-30 (CBE-30) supplement, and notification low means a CBE-0 supplement or annual report"	Revise the relevant CFR chapters and FDA post-approval change guidelines to align with the classification framework in the current document	Based on the current regulations under 21 CFR 314.70 and 21 CFR 601.12, as well as the existing FDA guidelines for post-approval changes (e.g., "CMC Changes to an Approved Application: Certain Biological Products," June 2021), CBE-0 supplements are intended for "moderate impact" level changes, and only annual reports are intended for "minimal impact" changes. It is proposed to revise these regulations and CFRs to indicate that CBE-0 is applicable for "minimal impact" changes.
96-130	Requirements to include statements regarding proposed ECs both in the Cover Letters and Module 3.2.R	We suggest changing to require the provision of these statements in only one location (e.g., 3.2.R), not both .	The requirement to provide identical statements regarding the implementation of ECs in both the Cover Letters and Module 3.2.R appears to be redundant. Provision of this information in one location (e.g., Module 3.2.R) should be sufficient.
270-280	The entire Section 7 "Maintenance of the Application"	Consider removing this section.	Up-to-date analytical procedures should be maintained at manufacturing sites and be made available during site inspections. There should be no requirement to submit them in an annual report (unless the changes impact ECs). The expectation to submit analytical procedures in Annual Reports essentially makes all analytical procedure parameters ECs, which is not the intended outcome of ICH Q12.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
406	Decision tree without “Annual Report”	Add “Annual report”	Add “Annual Report” as another reporting category for ECs of combination products.
305-315	Manufacturing site specificity of ECs	Consider removing or rewording	It is anticipated that ECs will apply generally to the product, given their relationship to parameters or attributes already demonstrated to be important. As such, the default position should be that these are applicable across all manufacturing sites. Only exceptions to this should be highlighted (for example, when there are concerns with site PQS, or when there are significant changes to manufacturing process and underlying Control Strategy as alternative of the existing approved process and site(s)).
151	“When proposing specific ECs, applicants should include a scientific justification for their selection in the relevant parts of module 3 of the application. In this justification, applicants should address both the identification of particular parameters or attributes as ECs and the proposed reporting categories (if applicable).”	“When proposing specific ECs, applicants should include a scientific justification for their selection in the relevant parts of module 3 of the application. In this justification, applicants should address both the identification of particular parameters or attributes as ECs and **provide** the **justification of** proposed reporting categories (if applicable). **The specific proposed reporting categories should be detailed in the PLCM document with cross-references to supporting data and justifications in Module 3**”	Reporting categories should not be required to be provided in Module 3.2.S or 3.2.P documents, since this will bring a degree of regional divergence to these documents and place an additional burden on the applicants. While it may be appropriate to discuss ECs and their relative risk classifications with relation to change in the body of Module 3, the discussion of final regional reporting categories should be reserved for the PLCM in 3.2.R (with cross-references to 3.2.S and 3.2.P as applicable)