Parenteral Drug Association

Connecting People, Science and Regulation®

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Anthony Ridgway
Biologic & Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
100 Eglantine Driveway, Tunney's Pasture
Ottawa, Ontario
K1A 0K9

Reference: Request for Comments on ICH Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, Q12, Draft version 16 November 2017

Dear Dr. Ridgway:

PDA appreciates the opportunity to respond to the draft ICH Q12 guidance "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management". PDA applauds the overall intent outlined in ICH Q12 and the emphasis put on concepts discussed and envisioned in ICH Q8 through to ICH Q11. Particularly, PDA is especially pleased to see language related to post approval change comparability protocols (PACMPs), the importance of an effective pharmaceutical quality system (PQS), risk-based approach to changes, leveraging process and product knowledge to negotiate Established Conditions (ECs) and reduction in the number of regulatory submissions. In addition, this proposal and framework for a harmonized approach with respect to technical and regulatory considerations for lifecycle management and use of the product lifecycle management (PLCM) document is most welcome.

If implemented as intended by regulators and industry alike ICH Q12 can help facilitate enhanced continual improvement and innovation and reduce the number of drug shortages that today are aggravated by the global regulatory complexity, including the ICH regions.

PDA wishes to offer specific comments related to improving the usefulness of the draft guidance. Key points include:

- Concerns with the language that discusses the fact that in certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to certain aspects proposed in this draft guidance. PDA is specifically concerned that consideration of legal frameworks provides no guarantee of modification and therefore will dampen the harmonization effort and fail to reduce the regulatory burden for both regulators and industry. Regulatory processes across the ICH regions need to

be harmonized to ensure that post-approval changes can be implemented in a timely manner for global distribution; this will allow for the maximum efficiencies intended by this guideline, and ultimately, for the benefit of patients.

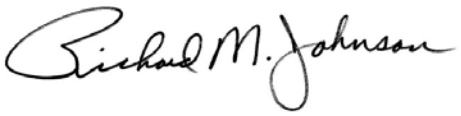
- Introduction of lesser known or new terms like Key Process Parameters (KPPs) and implicit established conditions and explicit established conditions (ECs) may lead to unnecessary confusion and overly complicate the utility and intent of ECs. ECs are intended to provide understanding and agreement between MAH and regulatory authorities on the parameters necessary to assure product quality; these parameters can change with knowledge gained throughout the lifecycle of the product. Stating that the KPPs should be ECs and/or trying to discern between implicit and explicit ECs is considered to add further complexity to this overall intent.

- Consideration should be given to pulling Appendix 2 (which describes the principles of change management and the importance of the PQS) forward as part of the main text of the document. There is important information in Appendix 2 that is crucial in the management of post approval changes; if left in an Appendix it is feared that the information won't be leveraged as it should be.

PDA is a non-profit international professional association of more than 10,500 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing, quality systems and regulatory affairs including members representing our Board of Directors, the Regulatory Affairs and Quality Advisory Board and the Post Approval Changes Task Force.

If there are any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President and CEO, PDA

Cc: Denyse Baker, PDA; Tina Morris, PDA

ICH Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
Draft version, endorsed 16November2017

General Comments	Rationale	Critical Y/N?
PDA welcomes the emphasis in the proposed ICH Q12 Guidance on ICH Q10 and the PQS. The guidance is positive in providing opportunities for changes to ECs through post-approval regulatory submissions, PACMPs and approved Post Approval regulatory commitments. The proposed guidance refers to predictability of information to support a CMC change and the information required to support that change. The emphasis on risk-based categorization and convergence for post-approval changes is commended; however, there is limited emphasis on harmonization or convergence on the change categories or filing types. The proposal for categories of prior approval and notification is a start, however this may lead to differences in regions for how information is filed given the guidance still allows that the types of changes are driven by regional regulations. Specific jurisdictions may need to update legal frameworks for harmonization to be truly recognized, if local jurisdictions are not able or willing to do this harmonization will be hampered. Reference is made to Page 1, Paragraph 4 (Line 81); with this paragraph both the principles outlined in ICH Q12 and in regional/national	Page 1, 4th paragraph (Line 81) "In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions ('EC') referred to in Chapter 3 and with Product Lifecycle Management ('PLCM') referred to in Chapter 5 as outlined in this guidance. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under existing regulations in these ICH regions." Unfortunately, consideration of legal frameworks provides no guarantee of modification. Given that this text was specifically added at the behest of the European regulators, unless changes are made, global implementation of ICH Q12 will be challenging.	Y

regulatory post approval CMC guidelines will need to be followed. It is recommended that local/national health authorities put Q+As in place to guide the applicant in the interim to avoid even larger complexity including hindrance of innovation and continual improvement.		

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
ICH version - Page 1, Second Paragraph and Section 1.2 Scope *EU version* – Line 69 and 87	Promoting innovation and continual improvement in the biopharmaceutical sector, strengthening quality assurance and improving supply of medicinal products	Promoting innovation and continual improvement in the **pharmaceutical and** biopharmaceutical sector, strengthening quality assurance and improving supply of medicinal products	As outlined in Section 1.2 Scope, this guidance is applicable to NCEs and biopharmaceuticals. However, this 2nd paragraph on Page 1 only refers to the biopharmaceutical sector which could be misleading to readers	Y
ICH version- Page 1, Paragraph 4 *EU version*- Line 81	In certain ICH regions, the current ICH Q12 guideline is not fully compatible with the established legal framework with regard to the use of explicit Established Conditions... [and following text through line 85]	[delete text]	In line with general comments above, established conditions are a fundamental aspect of ICH Q12 and the value is limited if the text relating to regional implementation remains. Regional implementation is in contravention of harmonisation across the ICH regions and the text should be removed. Additionally, ICH M4Q already outlines the basic concepts of CTD sections that contain descriptions of the commercial process vs. CTD sections that provide development information to enable the review. ICH Q12 serves only to formalize this distinction.	Y

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
ICH version - Page 1, 5th paragraph *EU version*- Line 90-91	”Changes needed to comply with revisions to Pharmacopoeial …guideline”	Delete sentences “Changes needed to comply with revisions to Pharmacopoeial …guideline”	It is not well understood why phamacopoeial changes are excluded from the scope of the guideline, even if in some cases, these are not harmonized between the regions. On the contrary pharmacopoeial changes could be regarded as minor changes to be reported as a notification only or could even be handled internally by the PQS as long as the registration dossier refers to the “current pharmacopoeial monograph”.	N
ICH version - Page 3, last paragraph, last sentence *EU version* - Line 166	An inspection may be associated with such changes.	[delete text]	Very few CMC changes lead to inspections (for example very complex changes that would typically include the addition of a new site). This statement is therefore unnecessary.	N
ICH version - Page 5, Third Paragraph, *EU version* - Line 216	Implicit ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance related to post-approval changes.	Delete “ECs in a submission are either implicit or explicit: Implicit ECs are elements that are not specifically proposed by the MAH but are derived from and revised according to regional regulation or guidance	The concept of explicit and implicit ECs is not necessary. ECs will be negotiated based on scientific rationale and product knowledge by the MAH. Gains under Q12 will be maximized through alignment on ECs with all agencies. If each agency can apply their own perspective of what implicit ECs must be added to the sponsor-identified ECs, there is greater opportunity for global non-alignment.	Y

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
		related to post-approval changes."	We believe that the notion of implicit ECs will cause confusion and lead to non-harmonization. ECs should be aligned and agreed upon between the MAH and Health Authorities during initial marketing application review. The MAH should not be held to implicit ECs that are not documented in the application. ECs are comprehensive in nature and include all the agreements between the Health Authority and MAH. This should remain the key paradigm of harmonization that will support the intent of the ICH Q12 document.	
ICH version - Page 5, 10th paragraph *EU version* - Line 233	The extent of ECs may vary based on the firm's development approach and potential risk to product quality.	The extent of ECs may vary based on the firm's development approach and potential risk to product quality. Prior knowledge may be used for defining ECs, particularly for marketed products.	Clarity for use of prior knowledge.	N
ICH version - Page 5, starting last paragraph	These should include critical process parameters (CPPs, as defined in ICH Q8(R2)), as well as key process parameters	These should include critical quality attributes, critical process parameters (CQAs and CPPs, as defined in ICH	Introduction of another term, key process parameters (KPPs), convolutes identification of established conditions (ECs). As stated earlier in the document, ECs are intended to provide	Y

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
EU version - Lines 239-242	(KPPs), which are parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality.	Q8(R2)), as well as parameters of the manufacturing process that may not be directly linked to critical product quality attributes, but need to be tightly controlled to assure process consistency as it relates to product quality.	understanding and agreement between MAH and regulatory authorities on the parameters necessary to assure product quality; these parameters can change with knowledge gained throughout the lifecycle of the product. Identification of ECs for a manufacturing process can be identified without introduction of a new term, and the term KPP does not add value in discerning them. The focus here should be on understanding and identifying ECs and appropriately linking them to an agreed post market plan and regulatory oversight. Introduction of a new term, KPP, can also create an additional barrier in realization of adoption of Q12 as a global standard, as MAH and Health Authorities try to align on what the term means (what is and is not a KPP) versus focusing on established conditions.	
ICH version - Page 7, Figure 1 *EU version* – Figure 1	Is the process parameter either a CPP or KPP?	Is the process parameter either a CQA or CPP?	In line with comment above, introduction of a new term, KPP, should not be introduced in this guideline.	Y
ICH version - Page 8 5th paragraph,	Where the relationship between method parameters and method performance has	Where the relationship between method parameters and method	This additional language aligns with the text contained within ICH Q2, where system suitability should be included when it is an	Y

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
EU version - Lines 295-297	not been fully studied at the time of submission, ECs will incorporate the details of operational parameters including system suitability.	performance has not been fully studied at the time of submission, ECs will incorporate the details of operational parameters (including system suitability when they are an integral part of the analytical procedure). ~~including system suitability~~.	integral part of the analytical method validation, but this may not always apply. A significant trend towards health authorities requiring MAHs to add many system suitability tests to analytical methods has been observed recently. Additionally, "system suitability" is a term most often associated with chromatographic methods and may not be appropriate for all method types and may not be considered an integral part of the analytical procedure. Additionally, EC should be associated with method performance outcomes, NOT the number of replicates or tests used to ensure that the equipment delivers these outcomes.	
ICH version - Page 13, Chapter 6, *EU version* - Line 484	--	ADD to beginning of Chapter: As per ICH Q10, companies that apply the principles and concepts of ICH Q8, Q9 and /or Q10 should be eligible for reduced regulatory oversight when they can demonstrate that an effective PQS is in place.	This section should provide more details about what constitutes an effective PQS. This is fundamental because demonstration that the company has an effective PQS is the main foundation for enabling less regulatory reporting of certain post-approval changes. With sufficient product and process knowledge and process understanding and the use of quality risk management, certain changes may be managed and documented within the PQS only as a regulatory notification, with no prior	Y

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
			approval by regulators, when a comprehensive risk assessment concludes that a proposed change introduces no additional risk to patient safety, nor to product quality and efficacy. The effectiveness of the Change Management system of a company can be demonstrated by quality standards that monitor the performance of the key elements of a PQS. Appropriate performance indicators, based on the use of data and trends, should be in place for each key element of a PQS; they should be meaningful, simple, and not subject to interpretation.	
ICH version - Page 14, 2nd paragraph *EU version* - Line 502	Changes to ECs should be communicated in a timely fashion between the MAH and the regulators, and between the MAH and the manufacturing chain (and vice versa).	Changes to ECs should be communicated in a timely fashion between the MAH and the regulators, and between the MAH and the manufacturing chain (and vice versa). Any change to a dossier that is not related to ECs can be managed in the company's PQS, and such changes to the dossier can be reported to the annual report as necessary.	It should be clarified that only changes to ECs should incur reporting. Other changes that are non-EC should not be reported.	N

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
ICH version - Page 14, last paragraph, *EU version* - Line 525	8. Post-approval changes for marketed products	8. Analytical Method Changes	Suggest changes to the title of this section, and make it a stand-alone chapter in order to clarify the intent of this section.	Y
ICH version - Page 14 last paragraph, *EU version* - Line 529	This chapter describes a strategy for a structured approach for frequent CMC changes (e.g., analytical methods) and data requirements for CMC changes (e.g., stability).	This chapter describes a strategy for a structured approach for changes to analytical methods.	Same as above, the description of the chapter is distracting to the intent of the chapter. Suggest clarifying that this chapter is dedicated to common/frequent analytical procedure changes.	Y
ICH version - Page 18, 5th paragraph, *EU version* - Line 647	8.2 Data requirements to support CMC changes	9. Data requirements to support CMC changes	Renumber to align with changes proposed above.	N
ICH version – Page 19, *EU version* - Line 675	9. Glossary	10. Glossary	Renumber to align with changes proposed above.	N
ICH version - Page 20 *EU version* -	10. References	11. References	Renumber to align with changes proposed above.	N

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
Line 676				
ICH version - Page 15, first paragraph *EU version* - Line 532	8.1 Structured approach to analytical procedures: Marketed products have existing analytical procedures that may benefit from advances made in analytical sciences. The intent of this chapter is to incentivize structured implementation of equivalent analytical procedures that are fit for purpose. An approach wherein specific criteria are defined for changes to analytical procedures used to test marketed products is described below. If this approach is followed and all criteria are met, the analytical procedure change can be made with immediate or other post-implementation notification, as appropriate, to the relevant regulatory authorities.	8.1 Structured approach to analytical procedures: Marketed products have existing analytical procedures that may benefit from advances made in analytical sciences. The intent of this chapter is to incentivize structured implementation of equivalent analytical procedures that are fit for purpose (as replacement or as an alternative). An approach wherein specific criteria are defined for changes to analytical procedures used to test marketed products is described below. If this approach is followed and all criteria are met, the analytical procedure change can be made with immediate or other post-	This suggestion for a structured approach to analytical procedure changes is applauded and in line with the goals envisioned of ICH Q12. To clarify, though a similar approach could apply for even more complicated methods as described in the bullets, the type of filing may be different and not subject to notification.	Y

Comments on Specific Items				
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	The following situations are out of scope of this chapter: …	implementation notification, as appropriate, to the relevant regulatory authorities. There may be certain situations in which a similar approach can be taken however, the change may require alternative validation approach and/or may not be considered a notification given the potential impact the change in method may have on product quality. Specifically, the following situations may not be considered notifications and require prior approval before implementation: …		
ICH version - Page 15, 2nd Paragraph, *EU version* - Line 539	The following situations are out of scope of this chapter:	Add note to this section. Note: while the scope of this section does not apply to all methods described herein, alternative approaches can be used to	As currently written, the scoping language incorrectly implies that the principles of ICH Q12 would not be applicable or implementable to those test methods listed.	Y

Comments on Specific Items				
Line No.	**Current Text**	**Proposed Change**	**Rationale**	**Critical Y/N?**
		meet the intent of ICH Q12.		
ICH version - Page 15, 8th paragraph, *EU version* - Line 560	Validation results should demonstrate that the revised method is equivalent to or better than the original method	Validation results or other performance indicators should demonstrate that the revised method is equivalent to or better than the original method	Not all method changes require revalidation of the method, particularly minor changes.	N
ICH version - Page 16 first paragraph *EU version* - Line 568	System suitability requirements should be established for the revised method. System suitability…"	System suitability requirements should be established for the revised method, when an integral part of the analytical procedure. System suitability…"	This aligns with the text in ICH Q2.	Y
Appendix 1	3.2.A.1 Facilities and equipment – Regional regulation and guidance apply	3.2.A.1 Facilities and equipment – Supportive information	The 3.2.A.1 section is included in CTD to provide supporting information about the facilities and equipment used in manufacturing the drug substance and drug product. ECs for the product should be incorporated into other sections of Module 3 such as the process description rather than being included in an Appendix section. Reporting of equipment and facilities changes should be required only if the	Y

Comments on Specific Items				
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			ECs in Module 3 sections such as the process description are impacted. Changes that impact only the supporting information provided in the appendix should not trigger reporting but rather changes to ECs in other sections may result in updates to the supporting information in A.1.	
Appendix 2	--	Consider moving the information in Appendix 2 into the main body of the document to supplement the information provided in Chapter 6.	It has been seen with provision of ICH Q10 that the Appendix 1 included in that document was not implemented readily by regulators in the ICH region. As such, enhanced flexibility for companies demonstrating an effective PQS was not recognized as early on or consistently as it could have been. A similar concern exists for ICH Q12 and the important information captured in Appendix 2.	Y