Docket No. FDA-2018-D-1609 for "Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management; Draft Guidance for Industry; Availability."

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GENERAL COMMENTS ON THE DOCUMENT
Members of ICH have laid out an impressive document in ICH Q12 covering the lifecycle of a product to provide clear expectations for change management, encourage manufacturers to adopt prospective approaches for continual improvement and innovation. Consider discussion around product and process development and other pre-market authorizations activities prior to market authorization (e.g., early small-scale (pilot) manufacturing, scaling activities, stage gates, implementing change control and managing changes).
The development of this guideline is a welcome progression of the ICH vision and the Q8-Q11 guidelines. However, while previous guidelines have focused on harmonising current regulatory expectations, there are many elements of the Q12 guideline that are aspirational. Our concerns are that Q12 at this stage is not compatible with ICH principles. "Regional regulations", "regional guidance" and "regional recommendations" phrases are symptomatic of lack of harmonization. Given that Q12 is meant to be a harmonized guideline, these phrases are used far too much. The EWG is urged to do all it can to ensure that the necessary legislative updates are occurring in the impacted regions **before** agreeing to this guideline. Lines 129 to 150 could, therefore, then be removed and many other references to disharmony or regional implementation (e.g., Line 537) removed.
The guide involves many references to other ICH documents. It is suggested to use hyperlinks or to create a table for readers to easily refer back to the documents where the tool or document originate.
Consider adding a section (potentially in 3.2.2) on the relationship of ECs and design space to make it clear that, although a design space itself is an EC, Q8 still applies and movement within a design space is not a change to an EC.

GENERAL COMMENTS ON THE DOCUMENT
The purpose and use of the term **Key Process Parameter (KPP)** term should be clarified and amplified. There is already difficulty understanding CPPs. At time of application, process consistency has historically not been required (how is this assessed?), hence the need for KPPs is hard to understand both from a technical and regulatory viewpoint. In addition, it is, will be or could become another regulatory expectation not currently required, leading to yet a further increase in regulatory expectations analogous to CPPs from ICH Q8. The concept of 'tightly controlled' has no scientific validity unless it is linked to outcome (e.g., the CQA(s) it impacts). What is the relationship between 'tightly controlled' and a PAR? A potential outcome of using KPPs is that applicants will argue that process consistency is ensured without 'tight' control of process parameters and therefore there are no KPPs. The current guideline confuses the concepts of criticality that were established in earlier guidelines, specifically Q8. By discussing the use of control strategy to modify potential risk (Figure 1) the door is opened to further reduction in the identification of CPPs. The definition also states that KPPs are related to product quality. Since product quality is established through the use of CQAs, there will be a relationship of some sort between such parameters and the CQAs. This confusion is not helped since it is hard to understand in Annex 1 why some parameters become KPPs in the enhanced approach example. For example, it is not clear that a blend time of 15-25 minutes represents a key process parameter, meeting the criterion that it is 'tightly controlled', especially since the range of times was without significant impact on homogeneity. However, if the EWG is committed to KPPs, it is recommended there be a simpler definition and a clearer demarcation between CPPs and KPPs. CPPs are, by definition, critical. In order for it to be acceptable for an MAH to change a CPP purely by notification, Q12 should clearly state in the guideline that the risk associated with a CPP can be reduced through the control strategy, an apparent conflict with current understanding of Q8. The guideline should then make it much clearer that process parameters without direct impact on quality (i.e., impacting only process consistency) should be identified as KPPs and such a designation automatically results in their change classification being reduced to notification. We suggest a simpler definition of a **KPP – a parameter of the manufacturing process which is not critical to product quality but that needs to be controlled.** Reporting categories therefore become: CPPs: prior approval or notification KPPs: notification Non-ECs: not reported.
A **schematic representation of** PACMP in the document would be easier for the readers to comprehend its elements and overall process

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Since the PLCM document is terminated when the product is withdrawn from the market, the guideline should contain some direction on how this could be achieved. However, it should be made clear that product discontinuation does not require the submission of a revised PLCM document to describe this phase of the product lifecycle. Suitable wording could be added to Section 5.3.
The term 'reporting' is used on occasions when the guideline probably means 'submission'. Please distinguish between a 'submission' that requires a regulatory response and 'reporting' that can be 'for information only' and does not require a regulatory feedback These terms should be specifically defined and used consistently. Further, it may be appropriate to distinguish between 'reporting' (a notification which does not require response) and 'reporting category' which is the risk-based system that is the substance of this guideline. Glossary definitions would help. See for example line 628 where it is not clear whether it should be submission requirements.
If Annex 1 is retained, analytical examples should be provided as it relates to section 3.2.3.2, lines 256 to 272 and section 8.1
It is recommended that Section 8 be revised to describe the types of change, categories of change, and studies/data needed for assessing the effect of change. The content of Sec 8 is so much narrower than what the title, "Post-Approval Changes for Marketed Products," suggests. The types of change can include the most commonly occurring changes, e.g., site, manufacturing process, analytical, specification, packaging. Examples can be provided to illustrate different categories of change according to Sec 2. And the studies and data needed to assess the effect of change for each example can be described in a new appendix. Technical requirements for post-approval changes are in need of global harmonization. Q12 would be significantly more useful to industry and beneficial toward harmonization if this kind of guidance is included.
We applaud the inclusion of science-/risk-based approaches to stability testing in support of post-approval changes in Q12 Step-2. However, the guidance provided in Sec 8.2.1 is conceptual and high level and lacks specifics or examples. As a result, global acceptance of science-/risk-based approaches to post-approval stability testing may not be realized. It is recommended that a new annex – which can be part of the new annex suggested for Sec 8 above – be established to provide specifics and examples.

Specific Comments on the Text

Line Number	Current Text	Proposed Change	Rationale or Comment
14		Add **pharmaceutical industry**	The benefit is not only in the biopharmaceutical sector but in the pharmaceutical industry as a whole
23		Add '**Quality'** in front of risk management	Quality Risk Management principles (ICH Q9)
25-30	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 (ECs) referred to in Chapter 3 and with the Product Lifecycle Management (PLCM) referred to in Chapter 5 as outlined in this guideline. These concepts will, however, be considered when the legal frameworks will be reviewed and, in the interim, to the extent possible under the existing regulation in these ICH regions.	Delete these sentences.	We see ICH as a place for harmonisation and convergence. This paragraph does not support ICH goal on global harmonisation/convergence.
38		Recommend a clarification be provided in Sec 1.3, possibly as a new paragraph at the end of 1.3 or as a new subsection 1.4 regarding the issues identified on the right.	It is unclear if any or all of the tools/enablers – i.e., ECs, PACMP, PLCM – are expected in new MAAs/NDAs when Q12 is implemented. It is also unclear how ECs can or should be applied to MAAs/NDAs approved prior to Q12.
87	…for reporting according….	Should this be '**submission'**?	The term 'reporting' is used here, later 'submission'. Please distinguish between a 'submission' that requires a regulatory response and 'reporting' that can be 'for information only' and does not require a regulatory feedback These terms should be specifically defined and used consistently.
112	Regulatory authorities are encouraged…	Use of the principles established in this guidance enables the use of risk-based regulatory…	The wording should be more positive and be more imperative to realizing the goals of Q12.
127	In addition, the lowest risk changes….	In addition, the lowest risk changes, **that is to non-ECs,** are managed and documented solely within the PQS and are not reported	The discussions on post approval changes and revision of ECs lack consistency. Line 127 says that the lowest risk changes are managed within

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		to regulators but may be verified on inspection.	the PQS. Given that 162 states that 'any change to ECs necessitates a submission to the regulatory authority' the earlier 127 needs to make it clear that this does not apply to ECs. Also, there may be non-routine inspections where such changes are inspected.
175	Implicit ECs	This section should be reconsidered to ensure it will not lead to additional lack of harmonisation. A clearer definition would be helpful.	If implicit ECs are different in each region, many benefits of Q12 will be lost. Each submission will then have a different Module 3.
180	…and associated reporting categories.	Delete the phrase at the end of the sentence.	It should not be necessary to specify a reporting category at the time of submission: the applicant may not be wanting to include the EC in a change management proposal.
181	Unless otherwise specified…..	Delete sentence	All dossiers are likely to have a combination of both. However, the guideline says that it is not mandatory to identify explicit ECs. Since ECs are legally binding commitments, how can it not be mandatory to identify explicit ECs?
183	An MAH may use one or both….	Delete sentence.	Since implicit ECs are not specifically proposed but exist through regulation, it is clear that their identification is mandatory. So, the implicit approach is mandatory (and by implication from the following paragraph). Therefore, it is unlikely to be acceptable in a submission to identify only explicit ECs.
207	..from product and process understanding (i.e., their development approach)…	..from product and process understanding (**e.g., their development approach or manufacturing experience**)…	There should be a mechanism for bringing legacy products into Q12.
245	Figure 1	The figure should be developed to distinguish between moderate and low risk changes, and the subsequent reporting categories.	To leave both industry and regulators with ambiguity over what constitutes moderate or low risk, and then to state moderate risks may require prior approval will cause confusion and disharmony. Industry will be tempted to ensure risks are assessed as low while regulators may

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			feel obliged to require prior approval of anything ranked as moderate.
464	The PLCM document can be located in either the CTD Module 1, 2 or 3 based on…	The PLCM document can be located in either the CTD Module 1, or 2 based on…	The word 'either' does not fit when there are 3 choices. However, consistent with the examples given in the guideline Appendix and the current international use of Modules 1&2 we propose it be located in Module 1 or 2. Proposing location in Module 3 only is inconsistent with CTD principles since it would need to be summarised in Module 2.
485-497	• Changes to ECs should be communicated … • The timeliness of communication is driven by the impact of any …. • Process knowledge and continual improvement are drivers for change…. • The communication mechanisms regarding ….	• Process knowledge and continual improvement are drivers for • Changes to ECs should be communicated • The timeliness of communication is driven by the impact of any • The communication mechanisms regarding	We suggest: The 4 bullet points are listed in a more logical order
499-502	Regulatory assessment and inspection are complementary activities and their fundamental roles remain unchanged by this guideline. Facility-related information obtained on inspection should be available to assessors and the most recent PLCM document, when applicable, should be available to inspectors.		We recommend that Q12 EWG considers including an example on the interaction between assessor and inspector in appendix or considers developing training material for consistency during the implementation of Q12.
525	Procedures where the specification does not…	Procedures where the **acceptance criteria** do not…	Acceptance criteria seems to be what was intended.
534	Changes to predictive model…	Delete this sentence (or reword to accommodate changes that are already foreseen).	There are already multi-variate methods for which changes would be 'in scope'. If the change to the predictive model is with the 'scope' for what can be changed, it should be allowed. See for example EMEA/CHMP/CVMP/QWP/17760/2009 Rev2, Guideline on the use of near infrared

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			spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations
575	Changes to spectroscopic procedures should remain within same specific technology, e.g., UV to UV, NMR to NMR	Changes to spectroscopic procedures should remain within same specific technology, e.g., UV to UV, NMR to NMR. **However, a change of technology can be acceptable provided the method is shown to be fit for its intended purpose.**	As long as the method meets the needs for the measurement, it does not matter what technology is used. Alternatively, if the revised protocol uses a new technology or an advanced version of the instrument, clarification on expectations should be provided.
585	All validation characteristics relevant to the type of method being validated should be executed as described in ICH Q2.	Propose to replace "executed" with "**evaluated**"	Full revalidation of every characteristic may not be necessary.
612	If any criterion is not met, an assessment should be performed to evaluate the impact of the failure to meet the criterion on the validity of the method.	… validity of the method**. If the assessment shows that the method provides at least equivalent information and results in the same quality decision it can be considered acceptable.**	Addition of details when **the criteria are not met and assessment has been performed.** Alternatively, if the criteria are not met and assessment is conducted could the study be repeated with new acceptance criteria? Additional information on this in the guideline would be helpful for the reader.
616	If new or revised specifications….	If new or revised **acceptance criteria**…	Accepted criteria is consistent with the intent.
620	….no impact on safety, efficacy, purity, strength….	…no impact on safety, efficacy **or quality.**	Simplification and avoidance of tautology.
629	This may include the updated method description, the protocol, and the summary report of the validation	Delete "the protocol".	It is not usual to submit protocols. That is part of the internal documentation available at GMP inspections.
668	KPP- …. critical product quality attributes	Delete 'product'	Consistency.
696	…. that can improve product performance	Change 'product' to '**process'**.	The intent of continual improvement is to improve the process to ensure the product meets the criteria agreed to in the application.
742	In addition to the requirements of ICH Q10…	In addition to the **elements** of ICH Q10	Q10 is a guideline not a regulation.

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778	Figure 1	Consideration should be given to a change management process that enables notification prior to implementation rather than prior approval (i.e. tell, wait and do).	
Page 25 CTD section column		Correct 3.3.P.4.3 to 3.2.P.4.3 Correct 3.3.P.4.4 to 3.2.P.4.4	Error in CTD numbering
Page 27 3.2.A.1		According to the notes for this table, we recommend to add (B) to indicate that this section is required for biotechnological/biological products only.	
Annex	There are several instances where it looks as though a design space could have been proposed.	Update some of the sections of the Annex to show what might be needed in the case of a design space being proposed.	It is vital that the concept of a design space is addressed so its utility is not lost.
Page 3	Roller Compaction Unit Operation		In Annex 1, it would be better if the example for the enhanced approach to roller compaction showed how the 'process understanding" could lead to flexible approaches to operating the process rather than listing ranges e.g. inclusion of a process algorithm. Where does an algorithm fit in ECs? How does this impact risk of change?
Annex II A and II B		Insert: **Less data or fewer batches can be justified, especially for small molecule drug substance, when the technology is transferred to a site of which the MAH has direct responsibility due to lower risks involved.**	One important risk factor for consideration in both examples is whether the alternate/recipient site is owned or contracted by the MAH. A case can be made that the risk is lower when the technology is transferred to a site of which the MAH has direct oversight and consequently less data or fewer batches can be justified, especially for small molecule drug substance.
Annex II.A.3, L75	In a comparative batch analysis….	Recommend revising this bullet to read, "In a comparative batch analysis, **one or more representative** batches of drug substance manufactured **at a pilot scale or above** at the alternative manufacturing site ….."	It is unclear why "three consecutive" batches are needed for comparative batch analysis and whether pilot-scale batches are acceptable.