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December 16, 2016

Dr. Hye-Na Kang
Department of Essential Medicines and Health Products
World Health Organization
1211 Geneva 27, Switzerland
kangh@who.int

Reference: WHO/PAC for BTPs Draft/3 Oct 2016-- Guidelines on procedures and data requirements for changes to approved biotherapeutic products

Dear Dr. Kang,

PDA appreciates the opportunity to comment on this draft guideline and applauds the efforts put forth here by the World Health Organization to align post-approval change expectations across many jurisdictions. This comes at a pivotal time, especially in light of the discussion around post-approval changes and the drafting of ICH Q12 and Pharmaceutical Life Cycle Management. The direction here will surely help worldwide jurisdictions improve, and even avoid, drug supply issues for important biotherapeutic treatments.

PDA recommends this guideline be fully aligned with concepts in ICH Q12 once finalized and with ICH Q10 Annex 1 '*Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches*'. Q10 states that when companies can demonstrate an effective PQS and product and process understanding, including the use of quality risk management principles they 'gain the opportunity to optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement'. Based on this PDA recommends that WHO ensure this guidance allows for leveraging the PQS for moderate changes where there is no increased risk to product quality, safety and/or efficacy by considering management such that implementation can occur unless the regulatory authority provides indication of concern within 30 days.

PDA recognizes that suggested review timelines for major and moderate changes align with the WHO vaccine document. However, biotech products are well characterized and should not require the same

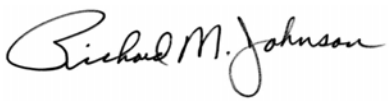
duration of review as complex vaccines. PDA therefore suggests that the proposed times in this draft could be shortened.

Finally, the guidance as currently written does not clearly address the post approval regulatory pathway for any improvements in potency assays for biotechnology products. This is a critical gap that should be addressed.

PDA is a non-profit international professional association of more than 10,000 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 and biological manufacturing including members representing the Science Advisory Board, the Regulatory Affairs and Quality Advisory Board, and Board of Directors.

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

Sincerely,



Richard Johnson
President and CEO, PDA

Cc: Denyse Baker, PDA; Richard Levy, PDA

Comments on WHO Working Document: WHO/PAC for BTPs 3 Oct 2016
Title of the document: Guidelines on procedures and data requirements for changes to approved biotherapeutic products

Comments submitted by: Parenteral Drug Association
Telephone number: 1-301-656-5900
Address: 4350 E West Highway, Bethesda MD 20814 USA
Attention: Department of Essential Medicines and Health Products (EMP)
Email : kangh@who.int.
Date : **16 December 2016**
*Kindly complete the table **without modifying the format** of the document - thank you.*

World Health Organization

Template for comments

General comment(s) if any :	**Originator of the comments**
In general, the effort put forth here by the World Health Organization to align post-approval change expectations across many jurisdictions is applauded. This comes at a pivotal time, especially in light of the discussion around post-approval changes and the drafting of ICH Q12 and Pharmaceutical LifeCycle Management. The direction here will surely help worldwide jurisdictions improve, and even avoid, drug supply issues for important biotherapeutic treatments. • Document should ensure alignment with ICH Q12 concepts once finalized. For example, the concept of Established Conditions would clarify post-approval change reporting categories. • PDA recommends this guideline be fully aligned with ICH Q10 Annex 1 '*Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches'* which states that when companies can demonstrate an effective PQS and product and process understanding, including the use of quality risk management principles they 'gain the opportunity to optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement'. Based on this PDA recommends that WHO ensure this guidance allows for leveraging the PQS for moderate changes where there is no increased risk to product quality, safety and/or efficacy by considering management such that implementation can occur unless the regulatory authority provides indication of concern within 30 days. • Recognize that suggested review timelines for major and moderate changes align with the vaccine document; however, biotech products are well characterized and should not require the same duration of review as complex vaccines. Suggest that the proposed times could be shortened.	

• Guidance for changes to QC tests excludes potency assays. The guidance as currently written leaves unclear the post approval regulatory pathway for any improvements in potency assays for biotechnology products. This is a critical gap that should be addressed.	

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification **L**= low **M**= medium **H**= high	Originator of the comments (for WHO use)
3	Page 6, Lines 10-13	The draft guideline makes it clear that plasma-derived products are in scope. Yet this definition of biotherapeutic product only seems to consider protein products prepared by rDNA technology. However, the term biotherapeutic product is used throughout the guidance to mean both rDNA and plasma-derived.	**Biotherapeutic product:** a biological medicinal product with the indication of treating human diseases that was developed and approved on the basis of the principles outlined in WHO guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology *(1)* or are plasma-fractionated products	M	
3	Page 7, Line 1	Critical Quality Attribute definition differs from ICH. Recommend harmonization of terms to avoid confusion.	Copy CQA definition from ICH: *A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.*	M	
3	Page 7, Lines 23-25	It is not clear why there a statement about risk of contamination in the definition of 'final batch'. There are also cases where several bulks are combined to produce the final batch, therefore consideration to remvoing the reference to "from a formulated bulk" should be given.	**Final batch:** a collection of sealed final containers that is homogeneous with respect to the composition of the product ~~and the risk of contamination during filling~~. A final batch must ~~therefore,~~ have been filled ~~from a formulated bulk~~ in one continuous working sesión.	M	
4	Page 10, Line 20	With any change, ultimate impact to the patient should be considered, that would include both safety and efficacy. If efficacy is not a concern, that should be documented and justified with the changes accordingly.	…of the drug product as it may relate to the safety ~~or~~ and efficacy of the product.	L	
4	Page 10, Line 23	In certain jurisdictions, manufacturer can distribute Product(s) following submission of the supplement for a moderate change (e.g. FDA CBE and EMA Type Ib) submissions). Consideration for a similar approach may be warranted.	Changes that may potentially have a major ~~or moderate~~ impact require submission of a PAS to the NRA. Changes that may potentially have a moderate impact may be filed at time of implementation, but prior	H	

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			approval may not be necessary. NRAs may consider moderate changes to be reportable and MA holders must submit the file at least 30 calendar days prior to distribution of impacted product. The NRA should consider a mechanism for establishing such a mechanism for moderate changes. If the NRA deems that the change should be a PAS (i.e. has the potential to have major impact) the MA must comply and cannot implement the change until approval is granted.		
4	Page 11, Line 9	"…*by a major manufacturing change such as a change in production capacity or filtration or purification system*." Some of these examples after "such as" may not always be a major manufacturing change. For example, change 3c listed on page 35 correctly categorizes the addition of an in-line filtration step as "minor".	Delete examples: "…*by a major manufacturing change ~~such as a change in production capacity or filtration or purification system~~*."	M	
4	Page 11, Line 12	Not all chemical modifications will result in a new product.	Delete this example: *Certain major changes, such as changes in the amino acid sequence, ~~or other chemical modifications of the product,~~ or changes that result in differences in the product quality attributes that impact the quality, safety and/or efficacy of the product, may be considered a new product*	L	
5	Page 13, Line 10	In general, it can be agreed that these types of changes may require nonclinical and/or clinical bridging studies of some sort. However, there may be specific instances where the introduction of a new formulation or new presentation can be supported by previously completed studies or in a product that has already been shown to be bio comparable (e.g. a platform product) and a bio-waiver is justifiable. "(d) a new presentation (addition of syringes to vials)." As worded, development of a kit or convenience package by	The following are examples of manufacturing changes that will likely ~~should~~ require nonclinical and/or clinical bridging studies: (a) generation of a new MCB derived from a different host cell line; (b) a new dosage form; (c) a new formulation; and (d) a new presentation (including a syringe presentation in addition to the already approved vial presentation). If the MA holder has a sound scientific justifiable position for an approach that is alternative to a bridging study, this should be discussed with the NRA	M	

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		adding a normal syringe to an approved vial would require a bridging study.	on a case-by-case basis.		
6	Page 13, Line 31	In line with the comment above in Section 4. Consideration may be warranted for instances where a change has deemed as having "moderate" impact should be filed, but prior approval is not necessary and the change could be implemented within a certain timeframe and pending feedback from the NRA (e.g. FDA CBE-0 or EMA Type Ib).	The major ~~and moderate~~ quality changes should be reviewed and approved by the NRA prior to implementation of the change. NRAs may consider moderate changes to be reportable and MA holders must submit the file at least 30 calendar days prior to distribution of impacted product. The NRA should consider a mechanism for establishing such a mechanism for moderate changes. If the NRA deems that the change should be a PAS (i.e. has the potential to have major impact) the MA must comply and cannot implement the change until approval is granted.	M	
6	Page 14, Line 17	In a continued effort to ensure supply chain and mitigate drug shortage and in line with EU, Health Canada, and FDA guidance, NRAs should consider introducing mechanisms that make review timelines clear and consistent for PASs. It appears this is contemplated in Section 8.	The MA holder should submit a PAS and receive notification of approval from the NRA before implementing the change. NRAs should consider establishing a mechanism that allows for clear review timelines and a consistent means to ensure those timelines are met (see Section 8).	M	
6	Page 14, Line 33	In line with comments made above with respect to "moderate" changes. Consideration may be warranted for instances where a change has deemed as having "moderate" impact should be filed, but prior approval is not necessary and the change could be implemented within a certain timeframe and pending feedback from the NRA (e.g. FDA CBE-0 or CBE-30).	The MA holder should submit a supplement and receive an ~~notification of approval~~ acknowledgement of receipt and agreement with filing type from the NRA before implementing the change. NRAs may consider moderate changes to be reportable and MA holders must submit the file at least 30 calendar days prior to distribution of impacted product. The NRA should consider a mechanism for establishing such a mechanism for moderate changes. If the NRA deems that the change should be a PAS	M	

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			(i.e. has the potential to have major impact) the MA must comply and cannot implement the change until approval is granted.		
8	Page 19, Line 4	Suggest that in some instances, there may be product or disease types that warrant expedited or priority review status. NRAs should be encouraged to provide written procedures for when those specific mechanisms may be leveraged for life-saving medications, or to address an unmet need.	Therefore, NRAs should establish written instructions regarding the submission procedures and timelines with action dates (including identification of emergency use, expanded access, expedited and/or priority review, timelines and procedures for life-saving medications to address an unmet need) …	M	
8	Page 20, Lines 11-16	Clarity is required around what is actually meant here. Is this in relation to consequential changes, of a lower category? Or is this associated with changes that have already been implemented and documented internally which the Company are then being asked to report as part of a later major/moderate change?	…Minor quality changes that are related/consequential or impact an impacted dossier section (e.g. if the Release specification was updated via a minor change to tighten a specification but now a change is being proposed to loosen another parameter) to a moderate or major quality change should be summarized in the PAS. Any minor changes that have been implemented should be in the affected documents (e.g. Common Technical Document sections) and summarized with the filing of the next submission to the NRA. ~~if they were implemented after the submission of a previous supplement for a moderate or major quality change. For instance, a minor change such as narrowing of a specification should be included in a supplement for a moderate or major change which includes updated quality control release information~~.	M	
8	Page 20, Line 32	Suggest that each NRA that is able to accept the review and approval of another NRA, should, establish a list of which NRA they are willing to accept approvals from.	NRAs of product-procuring countries that decide to recognize the decisions of other NRAs should establish alternative regulatory procedures for expedited approval of changes based on previous	M	

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			expert review and approval by the NRA of the country where the biotherapeutic products or SBPs are licensed…accordingly, those NRAs should also create a list of the NRA approvals they will recognize.		
8	Page 23, Line 8	Suggestion	If the same change is applicable to multiple products, a separate submission is generally required for each product but the data may be cross-referenced. NRAs may also allow same change to be bundled into one submission for multiple products. When cross-references are made to information that has been submitted previously, details of the cross-referenced information should be indicated in the cover letter.	L	
8	Page 24, Line 4	Suggest that NRAs should also have procedures in place for issuing information requests and timelines for responses in instances where the review is not stopped (e.g. Health Canada Clarifax issuances and response times).	The NRA should establish procedures and timelines for the review of MA holder's responses to the notification in instances where information requests are sent and the review clock is not stopped and in instances of non-compliance in cases where the review is stopped.	M	
8	Page 25, Line 2	Comparability protocols can also be provided in the original submission	*For NRAs currently taking this approach, a new comparability protocol can be provided in the original submission. In addition, a comparability protocol, or a change to an existing one, requires submission of a supplement and approval prior to implementation because it may result in a lower reporting category…*	M	
8	Page 25, Line 5	For some MAH with multiple related commercial products and facilities, providing a family of comparability protocols can facilitate and expedite manufacturing improvements	*For some MAH with multiple related products and facilities, an expanded change protocol can be proposed the scope of which may cover multiple related products or facilities.*	H	
Appendix 1	Page 29, Review Timelines	In line with comments above, if a changes is deemed a "moderate" quality changes, the opportunity to file and	Procedures – ~~PAS~~ Prior Notification (i.e Notify no less than 30 days	M	

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	Table, Line 28	then implement the change pending acknowledgment (as opposed to approval) from the NRA may be warranted. This may be in situations where a Comparability Protocol was already reviewed and approved previously or where changes may have a bit more supporting documentation than a "minor" change but less than a "major" change. (E.G. like for like primary container closure component, but different supplier with slightly different dimensions, but no impact on head space).	prior to implementation Maximum Review Time ~~3 months~~ 30 days (acknowledgement of receipt from NRA must be achieved prior to implementation)		
Appendix 1	Page 30, Line 18	In line with comment above, suggest that each NRA that is able to accept the review and approval of another NRA, should, establish a list of which NRA they are willing to accept approvals from.	NRAs that procure biotherapeutics from countries other than their own are encouraged to establish alternative accelerated timelines for changes that have previously been approved by the licensing NRAs. Accordingly, those NRAs should also create a list of the NRA approvals they will recognize.	M	
Appendix 2 and Appendix 3	Page 32 and Page 48 and 66	The approach presented here, and aligned with existing Health Canada guidance, is clear and extremely helpful for MA holders.			
Appendix 2 and Appendix 3	Page 34, Change 1., Drug Substance Manufacturing, Supporting Data, #6 and Page 50, Change 30. Drug Product Manufacturing, Supporting Data #9	For some biologics, three consecutive batches may not be feasible. It is acknowledged that fewer than three may be acceptable, but manufacturing in a consecutive manner may not be practical or necessary. For example, if a platform process is used to produce multiple products, a single, representative batch may be justified.	Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches, or leveraging data from scientifically justified representative batches, or batches not necessarily	M	

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			manufactured consecutively, may be acceptable where justified and agreed by the NRA.		
Appendix 2	Page 34, Change 2.b	Condition 1 (change does not impact viral clearance) should not apply to a change in the cell culture process	Delete condition 1 from Change 2b	H	
Appendix 2	Page 34, Change 2.c	Noncritical change example is actually a principle; not a defined example. Duplication of a fermentation train could be non-critical.	*a noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product. Specifically, these can include* ~~*(e.g.*~~ *a change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of detection of adventitious agents or production scale)* ~~*; or duplication of a fermentation train)*~~	L	
Appendix 2	Page 35, Condition 3	Reference to antigen does not apply: *No change in the impurity profile of the antigen outside the approved limits.*	*No change in the impurity profile of the* ~~*antigen*~~ *final product outside the approved limits.*	H	
Apenndix 2	Page 35, Changes 5 and 6.	To clarify any change in the raw materials biological origin should be assessed under these conditions and supporting documentation. Suggest that this could be one type of change and examples of "change in supplier or source" could be listed. This keeps the focus on the impact to the component and not a registration of suppliers.	5. Change in ~~supplier of~~ raw materials of biological origin (e.g. change in supplier or source of fetal calf serum, human serum albumin, trypsin). ~~6. Change in source of raw materials of biological origin~~	L	
Apenndix 2	Page 39, Change 14b	Change 14b lists condition 10 as to be fulfilled: *Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.*	This text impedes utilization of new tests that are innovations that can improve the overall assurance of quality. As stated in ICH Q6B, the use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process. These limits, which are the	H	

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			responsibility of the manufacturer may be used to initiate investigation or further action. Under these circumstances, MAH should be encouraged to develop new tests methods and should not need prior approval. Delete Condition 10 and add condition 8from change 14b.		
Apenndix 2	Page 41, Change 18a	Change 18a is categorized as "major". Change 19f (widening of acceptance criterion) is categorized as "moderate". These two categorizations appear to be ~~are~~ inconsistent with each other. If quality is maintained in 18a as documented by the data then both changes could be considered moderate changes.	Adjust the category of change in 18a to moderate and add condition "Documented evidence that consistency in quality is maintained".	H	
Apenndix 2	Page 41, Change 18b and Change 18c	Addition (or deletion) of a new Critical Quality Attribute (CQA) in the control strategy	Control strategy is not defined in this document. As defined in ICH Q10, the control strategy includes both established conditions and components that are not included in a filing. Therefore, this change as written does not provide clear guidance for either the MAH or the DRA. Delete changes 18b and 18c	H	
Appendix 3	Page 54, Change 35b	Change 35b lists condition 8 as to be fulfilled: *Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.*	This text impedes utilization of new tests that are innovations that can improve the overall assurance of quality. As stated in ICH Q6B, the use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process. These limits, which are the responsibility of the manufacturer may be used to initiate investigation or further action. Under these circumstances, MAH should be encouraged to develop new tests methods and should not need prior approval. Delete Condition 8 from change 35b.	H	
Appendix 3	Page 58, Change 46a	Change 46a is categorized as "major". Change 47f (widening of acceptance criterion) is categorized as	Move change as described in 46a to change 47 and create new change 47h. Conditions to be fulfilled and supporting	H	

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		"moderate". These two categorizations are inconsistent with each other. The supporting data needed to widen an acceptance criterion can also support moving a change from end-product testing to upstream controls	data for 47h will be the same as 47f		
Appendix 3	Page 58, Change 18b and Change 18c	Addition (or deletion) of a new Critical Quality Attribute (CQA) in the control strategy	Control strategy is not defined in this document. As defined in ICH Q10, the control strategy includes established conditions and components that are not included in a filing. Therefore, this change as written does not provide clear guidance for either the MAH or the DRA. Delete changes 46b and 46c	H	
Appendix 3	Page 59, Changes 48 – 52	These are redundant with changes 20-24 and are therefore unnecessary	Delete changes 48-52	L	
Appendix 3	Page 61, Change 56. Drug Product Changes.	It is not clear why the change in supplier of a primary component container closure component would necessitate its own category when the changes in 53 or 54 would already address that. Suggest adding "change in supplier" to the text in number 53 where examples are listed and make the requirements the same. This keeps the focus on the impact to the component and not a registration of suppliers.	Delete this section and add "change in supplier" to examples in Change 53.	L	
		Please add rows as necessary (with "copy and paste" empty rows)			