Parenteral Drug Association

Connecting People, Science and Regulation®

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March 22, 2018

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: Chemistry, manufacturing, and Controls changes to an Approved Application: Certain Biological Products Draft Guidance for Industry
Docket: FDA-1995-D-0288

Dear Sir/Madam:

PDA appreciates the opportunity to respond to the draft FDA guidance "Chemistry, manufacturing, and Controls changes to an Approved Application: Certain Biological Products." PDA applauds the incorporation of concepts from the draft ICH Q12 guidance on the topic of post-approval change into the biologics guidance paradigm, particularly language related to comparability protocols, risk-based changes, and risk management principles. PDA appreciates that the wording in the draft guidance will allow for companies demonstrating an effective Pharmaceutical Quality System to benefit from reduced regulatory reporting as per ICH Q10 Annex 1. PDA wishes to offer specific comments related to improving the usefulness of the draft guidance. Key points include:

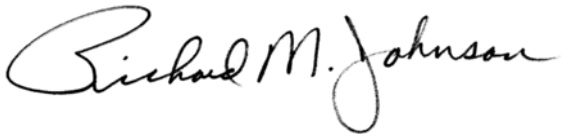
- The scope of the guidance should include specified biological products as well as biosimilars. Using the same guidance for products with a similar risk profile will be less confusing for companies with multiple product types in their portfolio.
- The Appendix of change examples, as well as the Special Considerations section, do not reflect the paradigm of a more risk-based approach to post-approval change (see specific comments on these sections).

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. The PDA PAC iAM task force is actively involved in promoting global harmonization for post approval change reporting and implementation to address concerns of drug shortages and barriers to innovation. This website, www.pda.org/pac highlights many of the resources developed by the task force and available to the public. PDA is willing to work with FDA in this arena to further the application of risk-based approaches and full implementation of the Q8, Q9, and Q10 concepts moving towards the goal of a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive, regulatory oversight.

These comments were prepared by a committee of experts with experience in pharmaceutical manufacturing, regulatory affairs and quality including members representing the Board of Directors, the Regulatory Affairs and Quality Advisory Board, and the Post Approval Changes for Innovation and Availability of Medicines Task Force(PACiAM).

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

Sincerely,



Richard Johnson
President, PDA

Food and Drug Administration Draft Guidance

CMC Changes to an Approved Application: Certain Biological Products

March 22, 2016

General Comments

General Comments	Rationale	Critical Comment? Y/N
PDA recommends that the agency change the product types included in the scope of this guidance. Specifically, page 3, section III. SCOPE should be modified to add specified biological products described in 21 CRF 601.2(a) as well as biosimilar products subject to licensure under section 351(k) of the PHS Act (42 U.S.C. 262(k)). Cellular and cell-based gene therapy products should be removed from the scope and covered by a separate guideline. PDA recommends that FDA incorporate the elements from Guidance for Industry – Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997) into this draft guidance. In some cases, the guidance for specified biologics is less conservative than the provisions in the draft due to product type. These less burdensome change provisions should be included using notes if necessary to designate the types of products eligible to use them.	Since 1997, advances in technology have changed which product types can be considered as similar enough to utilize the same general approach to post-approval CMC changes. PDA recommends that this guidance include "specified biological products" as well as biosimilars. As the guidance is already jointly issued between CBER and CDER and some provisions in the draft exclude certain product types, this change in scope should be possible. Using the same guidance for products with a similar risk profile will be less confusing for companies with multiple product types in their portfolio. Cellular and cell-based gene therapy products are significantly different than vaccines and naturally derived products such as enzymes and should be removed from the scope.	Y

Specific Comments to the Text

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Page 5, Section A (2)	In certain circumstances, the FDA may determine that, based on the Agency's experience with a particular type of moderate change, the supplement for such a change is complete and provides the proper information and particular assurances that the change has been appropriately submitted. The product made using such a change may be distributed immediately upon receipt of the supplement by the FDA (21 CFR 601.12(c)(5)).	In certain circumstances, the FDA may determine that, based on the Agency's experience with a particular type of moderate change, the supplement for such a change is complete and provides the proper information and particular assurances that the change has been appropriately submitted. The product made using such a change may be distributed immediately upon receipt of the supplement by the FDA (21 CFR 601.12(c)(5)). Based on scientific justification, these changes may be submitted as CBE-0.	Additional wording to clarify that a CBE-0 may be proposed by the holder is beneficial to both FDA and industry since it provides clarity on immediate distribution of materials impacted by the change.	N
Page 8, Section C. Submission of Changes to FDA, bulleted lists	[Current bullets do not indicated to include updated CTD sections]	Add bullet: Updated CTD sections	In accordance with the ICH M2 Expert Working Group eCTD specification guidelines, "International Conference on Harmonization of	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
			Technical Requirements for Registration of Pharmaceuticals for Human Use – Life Cycle Management", CTD sections should be lifecycled to reflect current information (established conditions).	
Page 8, Section C	Bullets indicating "Relevant validation protocols and data" and "A reference list of relevant standard operating procedures (SOPs)" as well as "A cross-reference to relevant validation protocols and/or SOPs"	Suggest identifying the requested information in line with the concepts of "established conditions" and "supporting information". Example change (proposed wording changes in italicizes): "The applicant is to include the following information in any supplement…. • A detailed description of the change • The products involved	Later in this same guidance document, the concept of "established conditions" is expanded upon. It would be useful to modernize the concepts of post-approval change management	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
		Information in support of the Established Condition: • The manufacturing site(s) or area(s) affected • A description of the method(s) … and data derived from these studies *Information included as supportive information:* • *Specific validation protocols and data* • A reference list of relevant standard operating procedures (SOPs)	throughout this document to provide a harmonized guidance and one that can withstand the global efforts to modernize, as led by the development of ICH Q12.	
Page 9, section E. Recommendations for Reporting Categories, third paragraph	"…a different selection may in some instances be deemed appropriate following discussion with the FDA."	"...a different selection may in some instances be deemed appropriate <u>based on scientific justification.</u>"	Per the concepts of ICH Q12, a risk-based approach to changes should be utilized. If scientific justification can be made in the filing to reduce the reporting category then a specific consultation with	Y

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
			FDA, e.g., a Type C meeting, should not generally be necessary.	
Page 10, 2nd paragraph	Some manufacturing changes may be reported in multiple categories…	Some manufacturing changes may be reported in multiple categories or impact multiple products…. When the same or multiple related changes impact multiple products, sponsors may choose to submit one dossier and cross-reference all impacted dossiers accordingly.	In order to save time and resource for both sponsors and the FDA, allowing the same data package/dossier for one impacted product be leveraged, where appropriate, for all impacted products should be an option.	Y
Page 10, Section F	Established Conditions are defined by the FDA as the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process	Established Conditions are defined by the FDA as the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process performance and quality of an approved	Legacy products may not have dossiers that identify Establish Conditions. PDA appreciates the clarification in this situation.	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	performance and quality of an approved product.	product, even if not specified as Established Conditions in the current license or registration.		
Page 11, Section V. Special Considerations	[Need for this section is unclear.]	[Delete this section. PDA recommends that the information in section V. sub-section A, "Changes in Process Parameters" be incorporated into the prior section on Implementing Changes to Established Conditions (Section IV, sub-section F) as this already addresses the evaluation needed when considering changes to the Established Condition (even if the original application did not include this descriptor), and supports the risk-based approach. PDA also recommends that the information in Section V, sub-section B, "Changes in Suppliers of Raw Materials" be deleted since the appendix already addresses raw material changes.]	Regarding sub-Section a, Process Parameters included in established conditions in the registration (or registered parameters for legacy products) should be subject to reporting based on risk. Non-registered or non-EC parameters are managed internally per ICH Q12. Changes to parameters within validated ranges also do not impact EC.	Y

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
			Regarding sub-section B, as there are existing examples of changes to RM and to suppliers of RM in the appendix, it seems more logical to keep them in one place and supplement the current list with additional examples that the Agency feels are important to address.	
Page 21, Appendix, Change in Drug Substance	Addition of a bioburden reduction or clarifying filter – CBE 30	Addition of a bioburden reduction or clarifying filter – AR	This has a very low risk of impacting the product quality, safety or efficacy,	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Purification Process, 3rd item			particularly in the purification process. These filtration steps are not even classified as KPPs and therefore would generally not be considered as part of the Established Condition.	
Page 22, Appendix, 3.2.S.2.3 Control of Materials – Changes to the source of starting materials and raw materials	Change in a source of starting material. NOTE: This type of change may in some instances (e.g., from tissue or plasma-derived to recombinant, from animal to plant, etc.) result in a separate BLA. Applicants should discuss with the appropriate FDA Review Division to determine the appropriate reporting category.	Change in source a low-risk or non-complex starting material or raw material (AR)	Per risk-based principles, changes to the source of a non-complex raw materials and starting materials, e.g., organic synthetic starting material, should not incur a PAS.	Y

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Page 22, Appendix, 3.2.S.2.3 Control of Materials – Changes to the source of starting materials and raw materials	Change in a source of a biological raw material	Change in a source of a high-risk raw material or starting material, e.g., a biological raw material (PAS) NOTE: This type of change may in some instances (e.g., from tissue or plasma-derived to recombinant, from animal to plant, etc.) result in a separate BLA. Applicants should discuss with the appropriate FDA Review Division to determine the appropriate reporting category.	Per risk-based principles, only changes to the source of complex raw materials or starting materials should incur a PAS	
Page 25, Appendix, 3.2.S.4 Control of Drug Substance	Adding, deleting, or replacing a test(s). Adding, deleting, broadening or shifting the approved acceptance criteria.	Deleting, or replacing a test(s). Deleting, broadening or shifting the approved acceptance criteria	Adding tests does not increase risk, similar to narrowing acceptance criteria and should be an AR	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Page 30, Appendix, 3.2.P.3.3 Description of Manufacturing Process and Process Controls	Scale-up of the manufacturing process at the formulation/filling/lyophilization stage. (PAS)	Scale-up of the manufacturing process at the formulation/filling/lyophilization stage using different equipment. (CBE-30) Scale-up of the manufacturing process at the formulation/filling/lyophilization stage using the same equipment. (AR)	Scale-up of a parenteral formulation is not as likely to impact CQAs as that of drug substance. If the same equipment is used, the scale-up impact is minor, consistent with FDA guidance *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997).	N
Page 35, Appendix, Facilities and Equipment	Addition or replacement of equipment of the same size and material of construction used in harvesting and pooling with no change in the process parameters specified in the approved BLA	Suggest deleting "used in harvesting and pooling"	It is not clear why this is only targeted for harvesting and pooling steps.	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
Page 36, Appendix, Facilities	Addition or replacement of a manufacturing facility for production of Drug Substance, Drug Product or intermediates.	Addition or replacement of a manufacturing facility for production of Drug Substance, Drug Product, or intermediates to a different company or where equipment and process are not similar (PAS) Addition or replacement of a manufacturing facility for production of an intermediate for the Drug Substance or Drug Product process where equipment and process is essentially similar and has appropriate cGMP inspection status (CBE-30) Addition or replacement of a manufacturing facility for production of Drug Substance, Drug Product or intermediates for which the new manufacturer is part of the same parent company or wholly owned subsidiary of the same company operating under the same Quality Management System	Allows for a risk-based approach where the higher risk instances (i.e. different company or different equipment/process) are PAS but the lower risk instances (i.e. similar equipment or process or within the same company) can be CBE-30	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
		and equipment is essentially similar and has appropriate CGMP inspection status (CBE30)		
Page 36, Appendix, Facilities	Addition or replacement of an existing packaging location (s) that does not have a CGMP status (i.e. no inspectional history)	[Keep current text and add these two additional provisions.] Addition or replacement of a primary packaging site that has previously been inspected by FDA (or other Agency where a Mutual Recognition Agreement for Inspection exists) and is under the same Quality Management System and equipment is essentially similar – CBE30 Change to or addition of a secondary packaging site that has previously been inspected by FDA (or other Agency where a Mutual Recognition Agreement for Inspection exists)- AR	Clarity in situations where there is less risk to product due to previous inspections and to promote harmonization	N
Page 37, Appendix, Facilities: Change	Addition or replacement of a testing laboratory for release or	Addition or replacement of a testing laboratory for release or	As noted in the current guidance	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
in the Testing location	stability testing by moving within an existing location (CBE-30)	stability testing by moving a test(s) to another laboratory at a location already qualified to conduct the test and already included in the license (AR)	(item 8) moving testing to another facility is a CBE30. Current guidance lists "Relocation of analytical testing labs between areas specified in the license" as Annual Reportable (item 3). The proposed wording clarifies that moving tests between labs already included in the license and already qualified to conduct the test presents very low risk to the product.	
Page 38, Appendix, 2nd row	Please clarify the need to have the parenthetical NOTE (i.e. (NOTE: This information should be provided as part of a complete submission for a new facility))	Suggest deleting NOTE.	It is not clear why the instruction that a WFI system should be part of a facility description for a new facility is included in a guidance on	N

Section Title/Paragraph or Sentence .	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
			changes to be reported.	