PDA Global Headquarters
Bethesda Towers
4350 East West Highway
Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

April 13, 2012

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

Reference: Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, Docket No. FDA-2011-D-0602

Dear Sir/Madam,

PDA is pleased to offer comments on the proposed Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. 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 biopharmaceutical product issues, including members representing our Biologics Advisory Board and our Regulatory Affairs and Quality Advisory Board. PDA appreciates the opportunity to offer comments on this proposed guidance and wishes to thank FDA for the opportunity to do so.

PDA reviewed the Draft Guidance on Quality Considerations along with the Draft Guidance on Scientific Considerations and the Draft Q&A guidance as they complement one another but our attached comments relate just to the Quality Considerations Guidance.

With regard to the proposed Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, we have provided detailed comments identified by line of the proposed guidance and have included a supporting rationale in the accompanying table. In addition to the comments provided in the attached document, PDA would like to highlight a number of additional issues that we believe are broader than the specific comments enclosed. First, we would propose FDA consider adding more explicit guidance around the generation of drug product. Second, we would propose FDA clarify the phrase "timeframes of actual use" at lines 290 - 291 as to whether it refers to the reference

products clinical use or testing data generation. Third, we propose FDA provide additional clarification regarding its thinking on the use of the term "finger print-like analysis" on lines 312 - 315.

Again, PDA appreciates the opportunity to comment on this proposed guidance document and provides these recommendations for your consideration. PDA believes that these comments will clarify and strengthen the final guidance to better serve the needs of both regulators and industry.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA

CC: Robert Dana, PDA
Rich Levy, PhD, PDA

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
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Line No.	Original Text	Proposed Change	Rationale
108-111	However, demonstrating that a proposed protein product is… by the product's sponsor.	Demonstrating that a proposed protein product is biosimilar to an FDA-licensed reference product manufactured by a different manufacturer will be more complex and likely require more extensive and comprehensive data than assessing the comparability of a product before and after a manufacturing process change made by the product's sponsor. This would be consistent with language used in the Scientific Considerations guidance line 181-183.	The guidance should be clear that because a biosimilar manufacturer will likely have a different manufacturing process from the reference product and have no direct knowledge of the manufacturing process of the reference product, the comparative assessment for a biosimilar will always be more extensive than for a manufacturer making a change to its own process.
274-277	Any differences in higher order structure …. should be evaluated in terms of a potential effect on protein function	Any **observed** differences in higher order structure …. should be evaluated in terms of a potential effect on protein function and stability.	
430-432	Tests used to characterize the product do not necessarily need to be validated for routine quality control purposes, but should be scientifically sound, fit for their intended use, and provide results that are reproducible and reliable.	Tests used for head-to-head comparative analytical assessment of the biosimilar and reference product do not necessarily need to be validated for routine quality control purposes, but should be scientifically sound, fit for their intended use, and provide results that are reproducible and reliable.	Guidance should be clear that analytical methods for comparative characterization of the product do not necessarily need to be validated for routine QC purposes; but that those used for release and stability assessment would need to be validated prior to submission of a 351(k) application.

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Line No.	Original Text	Proposed Change	Rationale
496-499	However, if the manufacturing process used to produce the proposed biosimilar product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary.	However, if the manufacturing process used to produce the proposed biosimilar product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies will be necessary.	The presence of different impurities or higher levels of impurities in a biosimilar product due to different manufacturing processes is a safety issue and the guidance should be clear about the need for additional pharmacologic/toxicological studies to address these differences.
505-507	The potential impact of differences in the impurity profile upon safety should be addressed and supported by appropriate data.	As a scientific matter, the potential impact of differences in the impurity profile upon safety needs to be addressed and supported by appropriate data.	The importance of differences in impurity profile between a biosimilar and a reference product on safety should be emphasized.