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July 5, 2016

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

Reference: FDA Draft Guidance: Assay Development for Immunogenicity Testing of Therapeutic Proteins
Docket ID: FDA-2009-D-0539-0024

Dear Sir/Madam:

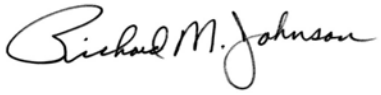
The updated version of this guidance document provides useful clarifications of strategies provided in the original 2009 guidance based on increased experiences with immunogenicity assays, and includes twice as many key literature references. PDA recognizes this draft adds information regarding immunogenicity assays for combination products and ADC's; points to information regarding immunogenicity assays for biosimilar products; and utilizes the current FDA terminology. It also clarifies the relationship of this guidance to animal immunogenicity assays and points to relevant guidance documents for those.

The tests proposed in the guidance are all looking at antibodies to the therapeutic protein and not other types of immune responses (eg. innate immune response) therefor PDA recommends that the scope statement be tightened to reflect this and has suggested language in the attached comments.

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 Regulatory Affairs and Quality Advisory Board, Post Approval Change Task Force, and Board of Directors.

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

Sincerely,



Richard Johnson

Cc: Denyse Baker, PDA; Richard Levy, PDA

Food and Drug Administration Draft Guidance

Analytical Method Development and Validation for Immunogenicity Testing of Therapeutic Protein Products

July 5th, 2015

General Comments

General Comments	Rationale	Critical Comment? Y/N
PDA recommends clarification that the scope of this guidance is antibodies to the therapeutic protein based on the tests proposed in the current draft. This clarification could be carried forward to throughout the guidance or clarified at the beginning as suggested below in specific comments to lines 21-23 and 57.	The tests proposed in the guidance are all looking at antibodies to the therapeutic protein and not other types of immune responses (eg. innate immune response). The scope of the statement should be tightened to reflect the type of tests proposed in the guidance.	Y
The updated version of this guidance document provides useful clarifications of strategies provided in the original 2009 guidance based on increased experiences with immunogenicity assays, and includes twice as many key literature references. It adds information regarding immunogenicity assays for combination products and ADC's. It points to information regarding immunogenicity assays for biosimilar products (and utilizes the current FDA terminology). It also clarifies the relationship of this guidance to animal immunogenicity assays and points to relevant guidance documents for those.		

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
21-23	For the purposes of this guidance, immunogenicity is defined as the propensity of the therapeutic protein product to generate **immune responses** to itself and to related proteins or to induce immunologically related adverse	For the purposes of this guidance, immunogenicity is defined as the propensity of the therapeutic protein product to generate ~~immune responses~~ **anti-drug antibody (ADA) immune responses** to itself and to related proteins or to induce	The tests proposed in the guidance are all looking at antibodies to the therapeutic protein and not other types of immune responses (eg. innate immune response). The scope of the statement should be tightened to reflect the type of tests	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	clinical events.	**ADA** immunologically related adverse clinical events.	proposed in the guidance	
57	The risk to patients of mounting an immune response to a therapeutic protein product	The risk to patients of mounting an **ADA** immune response to a therapeutic protein product	Better clarifies the scope of the guidance for testing to ADA. This clarification could be carried forward to throughout the guidance or clarified at the beginning as suggested above.	N
308	Similarly, for patient populations with a high incidence of RF, the sponsor should demonstrate	Similarly, for patient populations with a high incidence of **Rheumatoid Factor** (RF), the sponsor should demonstrate	Clarifies the abbreviation	N
309	Host cell proteins and other product-related impurities may interfere with demonstrating the assay specificity and selectivity as well.	If ADA's demonstrate cross-reactivity with Host cell proteins and other product-related impurities, the specificity of these immunogenic reactions should be further evaluated. ~~may interfere with demonstrating the assay specificity and selectivity as well.~~	Recently, case studies have shown anti-HCP antibodies to have clinical impact in some therapeutic products (CaSSS CMC Strategy Forum, Jan 2014, http://casss.site-ym.com/?CMCJ1513). If HCPs or other product-related impurities present in therapeutic products generate immunogenic responses in patients, those should be evaluated. ADA cross-reactivity with HCPs or other protein impurities in the product should not be simply considered 'assay interference'.	Y
318	For responses to other proteins, an unrelated protein of similar size and	PDA recommends deleting this statement. ~~For responses to other~~	The purpose of the assay is to detect antidrug antibodies made against a	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	charge can be used.	~~proteins, an unrelated protein of similar size and charge can be used.~~	unique epitope provided by the drug and since the matrix consists of thousands of proteins from serum or plasma it is not clear how the use of model drug proteins would provide information on specificity and selectivity of the assay. The model protein would require model epitopes present in the drug.	
388-391	Demonstrating assay precision is critical to the assessment of ADA because assay variability is the basis for determining the cut points and ensuring that low positive samples are detected as positive.	Demonstrating assay ~~precision~~ **repeatability** is critical to the assessment of ADA because assay ~~variability~~ **precision** is the basis for determining the cut points and ensuring that low positive samples are detected as positive.	For Bab and Nab assays the primary reported result is positive/negative for which traditional measures of precision (%CV, Stdev) don't apply. Assay signal precision is relevant to cut point but cut point can also be based upon a ratio of the negative control signal to the sample. Repeatability as defined as the consistency of the method to find true positives, positive and negatives, negative may be a more appropriate and relevant measure of assay performance for screening methods. Titer/concentration reporting versions of the methods would have more traditional precision related performance measures like %CV/Stdev but on concentration values rather than	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
			raw signal	
Line 846-848	"Assay validation is a process of demonstrating, by the use of specific laboratory investigations, that the performance characteristics of the ADA assay employed are suitable for its intended use.[23] "	Change the documents referenced in footnote 23 to remove *USP <1225> Validation of Compendial Procedures* and *ICHQ2(R1) Validation of Analytical Procedures: Text and Methodology.*	Although USP <1225> and ICHQ2(R1) provide definitions of the term 'validation', these guidances are only relevant to analytical methods to assess product quality; they are not applicable to immunogenicity assays. While the general principles of assay validation are broadly similar, the practices in those documents are substantially different due to the technologies employed and intended uses of the assays. Therefore the inclusion of these two references could mislead readers into trying to adapt practices from those guidances for immunogenicity assays, where they would not be suitable.	Y
Line 892	Samples should include negative controls and positive samples whose testing yields values in the low, medium, and high levels of the assay dynamic range.	Samples should **minimally** include negative controls and positive samples whose testing yields values in the low ~~medium~~, and high levels of the assay dynamic range **and negative control for assay background.**	We suggest changing the use of reference Ab in high, medium and low levels during validation to high, low and negative levels to coincide with the referenced document ShankarG, et al (2008)	

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
1028 - 1032	However, for patients receiving a therapeutic protein product at multiple times during the trial, the sponsor should obtain samples at appropriate intervals throughout the trial and also obtain a sample approximately 30 days after the last exposure. Obtaining samples at a time when there will be minimal interference from the therapeutic protein product present in the serum is essential. A sponsor should consider the therapeutic protein product's half-life to help determine appropriate times for sampling.	… the sponsor should obtain samples at appropriate intervals throughout the trial ~~and also obtain a sample approximately 30 days after the last exposure.~~ Obtaining samples at a time when there will be minimal interference from the therapeutic protein product present in the serum is essential. A sponsor should consider the therapeutic protein product's half-life to help determine appropriate times for sampling (e.g. **30 days after the last exposure.**)	Clarifies that 30 days is one possibility, but for post treatment sampling it is most important to take into account the half-life of the drug.	Y