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May 20, 2014

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

Reference: FDA Guidance for Industry Analytical Procedures and Methods
Validation for Drugs and Biologics
Docket [FDA-2014-D-0103]

Dear Sir/Madam,

PDA recognizes and appreciates that FDA has incorporated many elements of PDA Technical Report 57 *Analytical Method Validation and Transfer for Biotechnology Products* in this draft guidance, including the concepts for method comparability, the concepts for “pre-determined and justified”, and the approach to significant digits. PDA also recognizes the alignment with other existing standards such as USP <1224> and applauds the agency for moving towards greater harmonization.

PDA’s attached comments are focused on additional clarification that we believe will strengthen the document such as: when and how to apply the concepts of equivalence, non-inferiority, or superiority in comparison models; a clear statement of FDA’s intention to treat analytical methods previously approved in a marketing authorization (i.e. NDA, BLA, ANDA) in a similar manner to compendial methods when evaluating new and post approval change submissions; and inclusion of methods from pharmacopeia, other than USP, which are recognized by FDA (e.g. JP, EP) per MAPP 5310.7.

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 manufacturing including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

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

Sincerely,

Richard Johnson
President, PDA

CC: Richard Levy, PDA; Denyse Baker, PDA

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Analytical Procedures and Methods Validation for Drugs and Biologics
To be Submitted 20 May 2014**

General Comments	Rationale
<p>PDA recognizes and appreciates that FDA has incorporated many elements of PDA Technical Report 57 <i>Analytical Method Validation and Transfer for Biotechnology Products</i> in this draft guidance, including the concepts for method comparability, the concepts for “pre-determined and justified”, and the approach to significant digits. PDA also recognizes the alignment with other existing standards such as USP <1224> and applauds the agency for moving towards greater harmonization.</p>	
<p>PDA understands it is the FDA’s intention to treat analytical methods previously approved in a marketing authorization (i.e. NDA, BLA, ANDA) in a similar manner to compendial methods which includes providing references in new submissions rather than full description and managing process or method changes by verifying that the method is still suitable and completing a re-validation only if the verification is not demonstrated and recommends a general statement of this approach be added to section C. PDA also understands that this applies to methods in pharmacopeia, other than USP, which are recognized by FDA (e.g. JP, EP) per MAPP 5310.7. There are a few places in the draft guidance where the language is confusing or suggests requirements different from this approach. PDA recommends clarifying these to avoid confusion if someone were to read only one portion of the guidance out of context. Some examples are:</p> <ul style="list-style-type: none"> • Lines 86 and 125 should include additional FDA recognized sources (e.g. JP, EP) • Lines 88-89 and 308-311 should allow for compendial verification • Line 348 should not mention compendial methods because they may not require validation according to USP <1226> • Line 373 should allow for verification or revalidation 	

Specific Comments to Text

Line No.	Current Text	Proposed Change	Rationale
Line 46-50.	This revised draft guidance does not address...during development and validation.	Please add the following at the end of line 50: This guidance also is not intended to address analytical methods for combination products functional testing or microbiological methods validation.	Please clarify that these additional types of analytical methods are also out of scope for this guidance.
72-73	Each BLA must include a full description of the manufacturing methods, including	It should be:	Reference to ‘manufacturing methods’ is confusing in this context, as details about

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Line No.	Current Text	Proposed Change	Rationale
	analytical procedures	Each BLA must include a full description of the manufacturing process, including analytical procedures	the manufacturing process (3.2.S.2; 3.2.P.3) are documented in different sections than analytical methods.
77	For BLAs and their supplements, the analytical procedures and their validation will be submitted...	...procedures and their validation a comprehensive summary of the validation results will be submitted...	PDA understands that FDA reviewers need more detail than a one page summary of analytical methods however, providing the complete validation package would be burdensome on both industry and reviewers.
122-123	You should describe analytical procedures in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria.	You should describe analytical procedures in sufficient detail to allow a competent analyst to reproduce the necessary conditions and obtain results execute the method within the proposed acceptance criteria system suitability criteria	PDA recommends clarification so that the method can be evaluated based on its intended operation and not just on the results.
257-258	...analytical procedure is suitable for its intended purpose.	... suitable for its intended purpose, which is to consistently produce results that allow decisions about the article under test.	PDA recommends the addition of this language because the term “suitability for intended purpose” has no clear definition.
284-290	... temperature and humidity conditions	...temperature and humidity conditions. Existing stability results or development study results may be used for the stability indicating properties and do not need to be reproduced during validation.	PDA recommends this addition because the stability-indicating property of the analytical methods is typically established prior to method validation. Accelerated and stressed stability condition sample results are typically available by the time of method validation.
292-296	As the holder of the NDA, ANDA, or BLA You must submit -(1) the data used to establish that the analytical procedures used to meet proper standards of accuracy and reliability,...	As the holder of or applicant for an the NDA, ANDA, or BLA	PDA requests this clarification as the sentence is referring both to new applications and changes to approved marketing authorizations.

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362	In anticipation of life cycle changes in analytics, an appropriate number of samples should be archived to allow for comparative studies.	In anticipation of life cycle changes in analytics, the sponsor should consider retention of an appropriate number of representative samples to allow for comparative studies.	PDA is concerned about the ability of the sponsor to distinguish between method performance and sample stability especially if samples are retained early in development and may no longer be representative of the later commercial material due to degradation over time. This may not be needed in all cases especially if the product history is well controlled. Suggest taking additional samples during stability studies to be used for this purpose. This becomes less feasible further into the commercial lifecycle of a product.
442	Equivalence, non-inferiority, or superiority studies should be performed with appropriate statistical methods to demonstrate that the new or revised method performance is comparable or better than the original method.	<p>The analytical method comparability categories of equivalence, non-inferiority, and superiority, are described in ICH E9 and can be used for the comparison of method performance.¹⁻²</p> <p>Definitions</p> <p>Equivalence: <i>A comparison study to demonstrate that the results from two methods do not differ by more than the pre-specified lower and upper equivalence limits.</i></p> <p>Non-inferiority: <i>A comparison study to demonstrate that the results from the new method are not inferior (above non-inferiority limit) to the results of the old method.</i></p> <p>Superiority: <i>A comparison study to demonstrate that the results from the new</i></p>	PDA recommends replacing and expanding the text on method comparability as indicated here. This level of detail is needed to help the reader understand the difference between the approaches and how to apply them

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Line No.	Current Text	Proposed Change	Rationale
		<p><i>method are superior (above no-difference point) to the results of the old method.</i></p> <p>The method comparability category and the pre-specified limit(s) to establish equivalence or non-inferiority should be justified in the protocol. The superiority limit is typically set at the no-difference point and does therefore not require additional justification.</p> <p>For all qualitative tests (ICH Q2(R1) type I and IIb), a comparison of hit-to-miss ratios should be compared using a non-inferiority or superiority model. For a Detection Limit comparison, both hit-to-miss ratios can be compared at very low analyte concentrations using probability statistics.</p> <p>For all quantitative methods (ICH Q2(R1) type IIa and III), accuracy (lack of bias) and precision (intermediate precision) should be compared using an equivalence model. Although a significant bias in results may fail the equivalence test, the new method may be used when product specifications are appropriately changed.</p> <p>For stability-indicating methods, stressed samples and representative retains should be included. When establishing the sample types and numbers for paired testing, the statistical test(s), and pre-</p>	

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Line No.	Current Text	Proposed Change	Rationale
		<p>specified limit(s) and comparison model should be justified with respect to product specification and the historical manufacturing data.</p> <p>¹ ICH E9, Statistical Principles for Clinical Trials, 1998. ² PDA TR 57, Analytical Method Validation and Transfer for Biotechnology Products, 2012.</p>	
452	Analytical method transfer is typically managed under an internal transfer protocol that details ...	Analytical method transfer is typically managed under an internal transfer protocol that details	As written, the text is not clear what is required for transfers from one company to another. PDA recommends deleting the word “internal” as protocols will apply for any method transfers.
486	For certain biological products, samples ...	For certain biological products (e.g. vaccines and blood products), samples ... should be submitted with the BLA.	It is PDA’s understanding that submission of samples with the BLA is generally not required for Therapeutic DNA plasmid products; Therapeutic synthetic peptide products of 40 or fewer amino acids; Monoclonal antibody products for in vivo use; and Therapeutic recombinant DNA-derived products. PDA recommends clarifying which biological products are not included in this requirement per CFR 601.2(a).
Section X; line 494	REFERENCES	Add reference to PDA Technical Report 57 “Analytical Method Validation and Transfer for Biotechnological Products”	PDA recognizes that many concepts from the TR57 have been incorporated into this guidance and recommends a specific reference be added to allow applicants to easily find more detail and examples to illustrate these concepts.