



20 May 2014

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

*submitted via email*

Submission of comments on: **Docket No. FDA-2014-D-0103 Guidance for Industry  
Analytical Procedures and Methods Validation for Drugs and Biologics**

Dear Sir or Madam,

Thank you for the opportunity to comment on the proposed Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics. The draft Guidance was reviewed by ISPE members who welcomed the detailed directions on the content of analytical methods. ISPE is pleased to provide the following specific comments intended to add clarity to some areas of the document.

The International Society for Pharmaceutical Engineering (ISPE) is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE Membership. ISPE is committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators.

Thank you again for the opportunity to comment on the proposed draft Guidance. Please feel free to contact me if you have any questions

Yours sincerely,

Nancy S. Berg  
President/CEO, ISPE



*Proposed Regulation/Guidance Document:*

## **Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics**

Comments submitted by: **International Society for Pharmaceutical Engineering (ISPE)**

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### **GENERAL COMMENTS ON THE DOCUMENT (if any)**

This document is helpful in that it gives detailed directions on the content of analytical methods; it would be helpful if it could do the same for analytical method validation protocols and reports

### **Specific Comments on the Text**

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

<b>Line Number</b>	<b>Current Text</b>	<b>Proposed Change</b>	<b>Rationale or Comment</b>
100	...limits of detection (LOD) and quantitation limits (LOQ)...	...detection limits ( <del>LOD</del> ) and quantitation limits ( <del>LOQ</del> )	Consistent with ICH nomenclature,
140	...filter type....	...filter <b><u>surface area, membrane</u></b>	Type is ambiguous, surface area, membrane

Line Number	Current Text	Proposed Change	Rationale or Comment
		<u>type and pore size...</u>	type and pore size are the critical functions of a filter
148	<p>D. Reagents/Standards</p> <p>The following should be listed:</p> <ul style="list-style-type: none"> <li>• Grade of chemical (e.g., USP/NF, American Chemical Society, High Performance or Pressure Liquid Chromatography, or Gas Chromatography and preservative free).</li> <li>• Source (e.g., USP reference standard or qualified in-house reference material).</li> <li>• State (e.g., dried, undried, etc.) and concentration.</li> <li>• Standard potencies (purity correction factors).</li> <li>• Storage controls.</li> <li>• Directions for safe use (as per current Safety Data Sheet).</li> <li>• Validated or useable shelf life.</li> </ul>	<p>D. Reagents</p> <p>The following should be listed:</p> <ul style="list-style-type: none"> <li>• Grade of chemical (e.g., USP/NF, American Chemical Society, High Performance or Pressure Liquid Chromatography, or Gas Chromatography and preservative free).</li> </ul> <p><b><u>E. Standards</u></b></p> <ul style="list-style-type: none"> <li>• Source (e.g., USP reference standard or qualified in-house reference material).</li> <li>• State (e.g., dried, undried, etc.) and concentration.</li> <li>• Standard potencies (purity correction factors).</li> <li>• Storage controls.</li> <li>• <del>Directions for safe use (as per current Safety Data Sheet).</del></li> </ul>	<p>The first bullet is for reagents only, the rest of the bullets pertain to standards; requiring all bullets for both reagents and standards is not feasible</p>

Line Number	Current Text	Proposed Change	Rationale or Comment
		<ul style="list-style-type: none"> <li>Validated or useable shelf life.</li> </ul>	
182	...sensitivity solution (for impurity method) and standards	sensitivity solution (for impurity method), <b><u>selectivity/resolution solution (if required)</u></b> and standards	The target compound is spiked with impurities to check separation efficiency
191	...such as peak tailing, precision and resolution acceptance criteria...	...such as peak tailing, <b><u>number of theoretical plates</u></b> , precision and resolution acceptance criteria...	This is another helpful parameter to evaluate the column performance
194	...USP General Chapter <621> <i>Chromatography</i> .	Add: <b><u>Data to support system suitability acceptance criteria may be collected during the method development and robustness evaluation phases prior to formal method validation. This strategy will assure that an appropriate quantity of data is used to establish which system suitability parameters will be applied to support the method during validation and routine use.</u></b>	A suitable quantity of data will be needed to establish the most appropriate system suitability parameters needed to support the method.
226	...avoid added impurities and inaccurate analysis.	...avoid <b><u>contamination, degradation</u></b> , and inaccurate analysis.	To clarify text: “added impurities” is not clear and even confusing
245-249	For biological reference standards and materials, we recommend that you follow a	<del>For biological reference standards and materials, we recommend that</del>	The first phrase seems to be confusing. The second phrase is redundant, since the working

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	two-tiered approach when qualifying new reference standards to help prevent drift in the quality attributes and provide a long-term link to clinical trial material. A two-tiered approach involves a comparison of each new working reference standard with a primary reference standard so that it is linked to clinical trial material and the current manufacturing process.	<del>you follow a two-tiered approach when qualifying new reference standards to help prevent drift in the quality attributes and provide a long-term link to clinical trial material. A two-tiered approach involves a comparison of each new working reference standard with a primary reference standard so that it is linked to clinical trial material and the current manufacturing process.</del>	reference standard by definition qualified against the primary reference standard.
283	No text	<ul style="list-style-type: none"> <li>• <b><u>Robustness testing (if not already performed during development)</u></b></li> <li>• <b><u>System Suitability Verification</u></b></li> </ul>	<p>Important aspects of validation that are commonly overlooked</p> <p>Robustness should be footnoted appropriately to consider evaluating this parameter during the development phase of the method.</p>
316	(e.g. specificity, LOD, LOQ, precision, accuracy, etc.)	(e.g. specificity, <del>LOD, LOQ</del> DL, QL, precision, accuracy, etc.)	Consistent with ICH nomenclature, distinguishes DL from LOD (Loss on Drying)
343	Suitable software should be used for data analysis	<b><u>Software should be appropriately validated or output data should be independently verified to support the analysis.</u></b>	Although software validation is not directly part of the method validation, a reference to this parameter may be helpful.
364-367	For complex products that are sensitive to manufacturing changes, archived samples can be an important tool to make these	<del>For complex products that are sensitive to manufacturing changes, archived samples can be</del>	If the product has changed due to manufacturing changes, there is little value in going back to old samples to determine the

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	comparisons. The archived samples used in comparative studies should include samples that represent pivotal clinical trial material and marketed product.	<del>an important tool to make these comparisons. The archived samples used in comparative studies should include samples that represent pivotal clinical trial material and marketed product.</del>	continued validity of the method. The samples using the new process should be used in the re-evaluation.
384	Analytical method revalidation may also be warranted because of manufacturing process changes, such as an alteration in the drug substance manufacturing process that could impact method performance (e.g. route of synthesis, fermentation) or introduction of a new drug formulation.	<b><u>Revalidation should also be considered if the method will be altered to improve its performance during routine use.</u></b>	It is not uncommon during routine implementation of an analytical method to implement method improvements, e.g. HPLC column change, etc. that might be considered outside the validated state of the current method.
458	The comparative studies are performed to evaluate accuracy and precision, especially with regard to assessment of interlaboratory variability.	The comparative studies are performed to evaluate accuracy, <del>and</del> precision, <b><u>linearity, and quantitation limit</u></b> , especially with regard to assessment of interlaboratory variability	It's not uncommon that the receiving lab uses analytical equipment from different manufacturer. Linearity and QL need to be compared as well.