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Re: PDA comments on the Draft Guidance for Industry, Analytical Procedures and Methods Validation. **Docket No. 00D-1424**

PDA is pleased to provide these comments on the Draft Guidance for Industry, Analytical Procedures and Methods Validation. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality. A substantial number of our members companies will be affected by the implementation of this Guidance. Our comments were prepared by a group of international experts in this field.

General Comments:

PDA appreciates the initiative FDA has taken to update the "Guideline for Submitting Samples and Analytical Data for Methods Validation" from 1987. Since the last revision of the guideline, the ICH process has reached its first ten years of harmonization, which has developed into many new guideline documents harmonized between the three regions Japan, EU and USA. In addition, revisions of relevant FDA guidelines and general chapters of the USP have taken place.

Numerous references illustrate that the current draft guidance document contains issues that are also dealt with in other guidelines. For several of the guidelines referenced in the document, large parts of the text have been transferred to the current draft guidance. In some cases the text has been copied, in other cases the text has been modified when covering the relevant parameter or issue in this guidance, thus leading to inconsistencies. PDA is in favor of avoiding duplication and redundancy. When the duplicative text at a later time is changed in one guideline it must at the same time be changed in the other guideline in order to avoid inconsistencies, potential misinterpretations and non-compliance. In practice simultaneous updates may not occur.

FDA regularly recognizes the ICH harmonization process. In practice, ICH documents are implemented in the US regulatory framework. In some cases the current draft interprets or adds on to issues being covered in ICH guidelines already. An example of this is lines 428-429, section VIIA where the current text reads "ICH Q2A and Q2B address almost all of the validation

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parameters. Areas that should be provided in more detail are described below". PDA understands that there will be regional additions or differences to ICH guidelines and our desire is to keep those to a minimum. As will be seen from the specific comments, there are examples of the current draft being different from current ICH guidelines, we have attempted to bring these to your attention.

The draft document has extended its scope from "assist applicants in submitting samples and analytical data to FDA for methods evaluation" to "recommendations to applicants on submitting analytical procedures, validation data, and samples to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products." We suggest limiting the scope to that in the 1987 guideline. The guidance should focus on information to applicants to help facilitate testing at FDA laboratories. Information regarding content and format of an application, abbreviated application or applications for biologics licenses at the time of submission is found in 21 CFR 314.50, 21 CFR 314.94 or 21 CFR 601.2. In addition, the Common Technical Document (draft) specifies requirements for description of analytical procedures in sections S.4.2 and P.5.2.

PDA suggests to reference relevant guidelines instead of embedding or modifying text from the guidelines. That approach will be highly valuable for the industry. This would be in line with the approach used for the ICH Common Technical Document (CTD). In particular PDA suggests the following sections to be limited to references to other relevant guidances: VI Content and format of analytical procedures for NDAs, ANDAs, BLAs, and PLAs; VII Methods validation for NDAs, ANDAs, BLAs, and PLAs, Subsection A; XI Methodology.

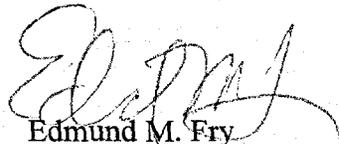
The current draft document is very comprehensive and in what PDA finds an attempt to develop a "stand alone" guideline on analytical procedures and methods validation it has become very detailed. The level of detail makes the document too prescriptive, thus leading to a mixture of regulatory and GMP issues in the same document. In addition, the level of detail might be restrictive to advances in analytical technologies.

PDA suggests the document to be less detailed and promote discussions between the applicant and the agency laboratories with respect to facilitating analyses at FDA.

The content of analytical procedures is being discussed in the draft guidance. PDA recognizes the importance of defining the minimum requirements for the content of analytical procedures. This subject would be an obvious area of interest for harmonization in the three ICH regions.

If you have any questions regarding our comments, or how we may assist with further development of the draft, please contact me.

Sincerely,



Edmund M. Fry  
President

Attachment: PDA comments on comments on the Draft Guidance for Industry, Analytical Procedures and Methods Validation.

Specific comments:

Lines 24-26, section I. Introduction:

Limit the scope to the original

Reason: The widening of the scope leads to redundancies. See also general comment

Line 122, Section III. C Stability-Indicating Assay:

Change text to "A stability-indicating assay is a validated analytical procedure..."

Reason: The word quantitative should be deleted as not all stability indicating assays are quantitative, e.g. SDS-PAGE.

Lines 128-129, Section III C Stability-indicating assay:

Delete the sentence.

Reason: The requirement is self-evident.

Lines 139-140, Section IV, A, Type of Standard:

Change wording to "...a reference standard should have a degree of purity depending on its intended use and be fully characterized"

Reason: Although, the requirement of "highest purity" is found in the 1987 document, ICH Q2B states "The degree of purity necessary depends on the intended use" (Section I). Q6A (draft) states "It has a quality appropriate to its use" (Section 2.11). Q6B states "...in-house primary reference material, prepared from lot(s) representative of production and clinical materials" (Section 2.2.1). The focus for reference standards should be characterization.

Lines 155-156, Section IV, C, Characterization of a reference standard:

Change wording to "A reference standard that is not obtained from an official source should be prepared from lot(s) representative of production and clinical materials, and it should be thoroughly..."

Reason: This is consistent with ICH Q6B (section 2.2.1), which means that the practice of "highest purity" should not take precedence over ICH requirements. See also comment above.

Lines 158-160, Section IV, C, Characterization of a reference standard:

Change wording to "...characterize a reference standard are expected to be different from and/or more extensive than, those..."

Reason: It is not always necessary that analytical procedures for characterization purposes differ from those used for routine QC analysis. The methods may be different and/or more extensive.

Lines 209-227, Section V, Methods Validation for INDs:

Add information from ICH Q7A, step 4, section 19.80 that states "While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound"

Reason: This reflects current thinking in the three ICH regions.

Lines 230-346, Section VI, Content and Format of Analytical Procedures for NDAs, ANDAs, BLAs, and PLAs:

We suggest changing the entire section back to the wording in the 1987 guideline.

Reason: The original wording has a satisfactory level of detail. With respect to the System Suitability Testing section (lines 271-288) it is suggested to delete the section and replace it by a reference to ICH Q2B (section X), USP <1225> Validation of compendial methods, USP <621> Chromatography and Reviewer Guidance. Validation of Chromatographic Methods (section IV.J), which all describe system suitability tests.

Lines 268-269, Section VI, D, reagents:

Delete "and usable shelf life for these reagents"

Reason: This is a GMP issue, which should not be covered by the guidance.

Line 286-287, Section VI, E, System Suitability Testing:

Delete sentence.

Reason: Blank titration does not indicate the correct performance of the instruments.

Lines 313-346, Section VI, J, Reporting of results:

Section J Reporting of results is suggested to be reduced to references to ICH Q3A® – Drug Substances) and ICH Q3B® – Drug Products) as well as USP (General Notices) with respect to rounding, significant figures and reporting of impurities.

Reason: ICH Q3A(R) and ICH Q3B(R) cover impurities in Drug Substances and Drug Products to a detailed level. The current drafted text is redundant as it should be up to the applicant to determine details of reporting impurities based on the ICH documents.

Lines 347-593, Section VII, Methods validation for NDAs, ANDAs, BLAs, and PLAs:

It is suggested that the entire section be replaced by a reference to ICH Q2A, ICH Q2B, FDA Reviewer Guidance - Validation of Chromatographic Methods and USP <1225> Validation of Compendial Methods.

Reason: The above mentioned documents/references discuss analytical procedures validation. In case there are suggestions for changes or additions to the ICH documents these should be forwarded to and handled by ICH EWGs.

Line 378, VII, A, Noncompendial analytical procedures, robustness:

It is suggested to delete robustness from the list.

Reason: it is not part of the corresponding list in ICH Q2A (section II), where it is stated "It should be noted that robustness is not listed in the table but be considered at an appropriate stage in the development of the analytical procedure"

Lines 380-427, VII, A, Noncompendial analytical procedures, Other methods validation:

Replace the entire section by a reference to ICH Q2B and the text from that guidance: "All relevant data collected during validation and formulae used for calculating validation

characteristics should be submitted and discussed as appropriate.”

Reason: The section is redundant when taking ICH guidances into consideration. Some of the content is found in ICH Q2B other in ICH Q3A(R) and ICH Q3B(R).

Lines 392-393, VII, A, Noncompendial analytical procedures, calculations:  
Delete the sentence.

Reason: This is a GMP issue, which should not be covered by the guidance.

Lines 428-521, VII, A, Noncompendial analytical procedures, validation in addition to ICH:  
Replace the section by a reference to ICH Q2A & ICH Q2B & USP <1225>.

Reason: ICH Q2A and Q2B and USP <1225> cover validation issues. Interpretations of other guidances and additions to these should be avoided.

Lines 431-438, VII, A, Noncompendial analytical procedures, Robustness:  
Replace the section by a reference to ICH Q2B.

Reason: ICH Q2B covers robustness in section IX.

Lines 395 & 439-454, VII, A, Noncompendial analytical procedures, Stress testing:  
Replace the section by a reference to ICH Q1A(R)

Reason: The ICH Q1A(R) guidance covers stress testing in much greater detail than the draft document does.

Lines 464-465, VII, A, Noncompendial analytical procedures:  
Change “Quantitation limit” to “Reporting threshold (Quantitation limit)”.

Reason: This is the wording in ICH Q3A.

490-491, VII, A, Noncompendial analytical procedures, Drug Substance  
‘The analytical...’ Delete sentence.

Reason: An analytical method must be appropriate for batches produced according to the registered process. It should detect differences between samples/batches of different quality, purity etc. but it is not intended, e.g. to detect process changes that do not influence product quality.

498-507, VII, A, Noncompendial analytical procedures, Drug Product:  
Delete the sentences.

Reason: This is too detailed, the specifics should be discussed between the firm and the agency.

Lines 507-508, Peak identification:

Replace the section by a reference to ICH Q3A(R)

Reason: Reporting of impurities is covered as a specific topic in ICH Q3A(R). This draft guidance suggests that “All responses (e.g. peaks) should be labeled and identified”. That is in contrast to ICH Q3A(R), which states that “Levels of impurities that are not more than (>) the

reporting threshold given in Attachment 1 need not be reported”.

Lines 512-513

Delete sentence.

Reason: An analytical method should detect differences between samples/batches of different quality, purity etc. but it is not intended, e.g. to detect process changes that do not influence product quality.

Lines 513-514

Change wording.

Change “Quantitation limit” to “Reporting threshold (Quantitation limit)”.

Reason: According to ICH Q3A (revision) the term ‘Reporting Threshold’ instead of ‘Quantitation Limit’ should be used.

Lines 522-546, Table on recommended validation characteristics:

Replace the section by a reference to ICH Q2A

Reason: Recommended validation characteristics are covered in ICH Q2A and ICH Q2B. The Table differs from that in ICH Q2A with respect to 1) Robustness is not part of ICH table; 2) The footnote related to specificity differs in applicability and 3) The column titled “Specific Tests” is not part of ICH Q2A

Lines 547-558, Identification:

Replace the section by a reference to ICH Q6A and ICH Q6B

Reason: Sections 4.1.2 and 4.2.2. in ICH Q6B and sections 3.2.1 (b) and 3.2.2 (b) in ICH Q6A covers identity.

Lines 559-565, Impurities:

Replace the section by a reference to ICH Q6A and ICH Q6B

Reason: Sections 4.1.3 and 4.2.3. in ICH Q6B and sections 3.2.1 (d) and 3.2.2 (d) in ICH Q6A covers impurities.

Lines 566-570, Assay:

Replace the section by a reference to ICH Q6A and ICH Q6B

Reason: Sections 4.1.4, 4.1.5, 4.2.4 and 4.2.5. in ICH Q6B and sections 3.2.1 (c) and 3.2.2 (c) in ICH Q6A covers assay.

Lines 571-580, Specific tests:

Replace the section by a reference to ICH Q6A and ICH Q6B

Reason: Sections 4.2.6. And 4.2.7 in ICH Q6B and section 3.3 in ICH Q6A cover specific tests.

Lines 586-587, Verification of compendial methods:

As 21 CFR 211.194(a)(2) states "suitability of all testing methods used shall be verified under actual conditions of use", it is helpful that the specific requirements regarding what constitutes verification be defined. PDA suggests that the specifics regarding verification are included in USP <1225>, which covers validation of compendial methods.

Reason: This will help clarify FDA's current thinking regarding verification of compendial methods

Lines 610-620, Comparative studies:

The wording should be defined in the Glossary. We suggest comparative studies to focus on either precision in general or reproducibility.

Reason: Clarifies the text. FDA Guidance for Industry. PAC-ATLS: Postapproval Changes – Analytical Testing Laboratory Sites also covers comparison when changing laboratory site.

Lines 628-645, Revalidation:

Replace the section by a reference to ICH Q2A and USP <1225> Validation of compendial methods

Reason: Revalidation is covered by the above mentioned documents

Lines 658-659

For "ANDA...application". It should be specified how many copies are needed.

Reason: 21 CFR 314.507i states that 3 copies are needed.

Lines 702-705

Change wording for the MSDS requirement

Reason: The requirement for a MSDS cannot always be met, e.g. for some impurity standard materials.

Lines 734-735, Shipment of samples:

Change text to read "...an amendment containing a copy of relevant parts of the batch record and certificate of analysis...".

Reason: It is not necessary to submit entire batch records that may be voluminous, only parts relevant to the testing should be submitted

Lines 740-741, Storage of bulk substances:

Change text to read "Bulk Substances... should be stored in containers that simulate the market container".

Reason: This is consistent with ICH Q7A section 11.52, that describes requirements for stability samples. Samples submitted to FDA should be stored like stability samples.

Lines 799-1095, Methodology:

Delete the suggestions for methodology as these are covered in USP and FDA Reviewer Guidance – Validation of Chromatographic Methods.

HPLC, GC is covered in USP <621> Chromatography;  
CE is covered in USP <727> Capillary Electrophoresis;  
Spectrophotometry, spectroscopy, spectrometry and related physical methodologies are covered  
in USP <851> Spectrophotometry and light-scattering, USP <736> Mass Spectrometry, USP  
<761> Nuclear Magnetic Resonance and USP <941> X-ray Diffraction;  
Optical rotation is covered in USP <781> Optical Rotation;  
Particle size analysis is covered in USP <786> Particle Size Distribution Estimation by  
Analytical Sieving and USP <788> Particulate Matter in Injections;  
Dissolution is covered in USP <711> Dissolution  
Reason: The section is redundant as most of the information is found in relevant USP chapters.  
In case the agency will define specific requirements for non-compendial methods regarding  
methodology, section H (lines 1073-1095) can be rewritten to take that into consideration

Line 832

Delete 'Recommended pH range for column use'

Reason: This is not useful information since the buffer pH is anyway fixed.

Lines 868-869

Delete 'The effect of... procedure.'

Reason: This is part of the 'Ruggedness' evaluation.

Line 883

Delete 'external diameter'

Reason: This not useful information.

Lines 913-926

Delete whole section

Reason: This is all self-evident.

Line 938

Delete 'external diameter'

Reason: This not useful information.

Lines 985-993

Delete whole section or indicate the topic 'enantiomeric excess' in header.

Reason: Self-evident.

Lines 1001-1003

Delete 'The normal... calibration.'

Reason: This is not useful information.

Lines 1028-1035

Delete whole section

Reason: This is not useful information.

Line 1066

Delete 'Both the dissolution and'

Reason: One can only validate the sampling and the analytical procedure.

Lines 1077-1079, Use of new instrumentation:

Delete the sentence in lines 1078-1079.

Reason: It is written that rare or exotic systems as well as automated analytical procedures may delay the validation process. This could potentially conflict with ICH Q6A and ICH Q6B which state "New analytical technology, and modifications to existing technology, are continuously being developed. Such technologies should be used when justifiable" (ICH Q6A, section 1.3) and "New analytical technology and modifications to existing technology are continually being developed and should be utilised when appropriate" (ICH Q6B, section 2.1).

Lines 1089-1095:

Delete the sentences.

Reason: See above for lines 1078-1079.

Lines 1113-1125.

The list is incomplete compared to the contents of the guideline. PDA suggests the list to be completed.

Reason: A completed check list will be useful.

Lines 1257-1263, Definition of Drug Substance/Active Ingredient:

Change the definition to that used in ICH Q6B.

Reason: Will harmonize the document with ICH document.

Lines 1274-1275, Definition of Reagent:

Change the definition to that used in ICH Q6A.

Reason: Will harmonize the document with ICH document

Lines 1277-1280, Definition of Specification:

Change the definition to that used in ICH Q6A or ICH Q6B.

Reason: Will harmonize the document with ICH documents.