

Food and Drug  
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AVI

**Comments on "Guidance for Industry: Analytical Procedures and Methods Validation". Docket No. 00D-1424 CDER 9867, FR Doc 00-22143.**

Dear Sir/Madam

We have read the suggested draft "Guidance for Industry: Analytical Procedures and Methods Validation. Chemistry, Manufacturing, and Controls Documentation" published August 2000 with great interest. We appreciate the possibility of submitting comments thus allowing for a dialogue between the agency and the industry. The following is our comments to the draft guidance. Comments are in the form of general comments followed by specific comments identified by line numbers. A copy of our comments is also e-mailed to [cunninghamp@cder.fda.gov](mailto:cunninghamp@cder.fda.gov) as suggested in the text.

**General comments:**

It is appreciated that the 1987 "Guideline for Submitting Samples and Analytical Data for Methods Validation" is being updated. Regular review and revision of guidelines can adjust and account for changes in other guidances, regulations, technological and scientific evolution as well as trends in CGMP. Since the issuance in 1987 at least 15 other documents of relevance to the current draft have been issued either in draft or final versions (ICH, FDA or Pharmacopoeias). These include ICH Q1A (R): Stability Testing of New Drug Substances and Products (2000); ICH Q2A: Text on Validation of Analytical Procedures (1995); ICH Q2B: Validation of Analytical Procedures: Methodology (1996); ICH Q3A (R): Impurities in New Drug Substances (2000); ICH Q3B (R): Impurities in New Drug Products (2000); ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (1997); ICH Q6B: Specifications: Test Procedures and

Acceptance Criteria for Biotechnological/Biological Products (1999); ICH Q7A: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (2000); ICH The Common Technical Document for the Registration of Pharmaceuticals for Human Use (2000); Reviewer Guidance. Validation of Chromatographic Methods (FDA, 1994), Guidance for Industry. PAC-ATLS: Postapproval Changes – Analytical Testing Laboratory Sites (FDA, 1998); Guidance for Industry. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (FDA, 1995); Guidance for Industry. INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products. Chemistry, Manufacturing, and Controls Content and Format (FDA, 1999)

The suggested draft guidance gathers information, which to some extent is found elsewhere in other guidelines or pharmacopoeias. This is primarily due to widening the scope compared to the 1987 guideline. That leads in certain sections to redundancy and to some extent item specific interpretations differing from other guidances. This should be avoided in order to avoid current and future inconsistencies between guidances. We therefore suggest to limit the scope to the the original scope in 1987, i.e. information that will facilitate analyses at FDA testing laboratories. This issue is further detailed under specific comments.

We suggest that the final document does not reference draft documents.

We welcome a common approach to a table of contents for Analytical Procedures. However, we suggest to include that as a topic for either ICH Q2A/ICH Q2B or a new ICH Q2C. This will harmonize analytical procedures within the three ICH regions.

We suggest the following sections to be limited to references to other relevant guidances, thus being removed from the final version of the document:

- 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

### **Specific comments:**

The specific comments are sorted by line numbers. References are made to the latest version of the document available to the public. In some cases we suggest to eliminate an entire section. However in case that view is not shared by the agency, in some cases we have also added specific comments within those sections.

#### **Lines 24-26, Scope**

*Suggestion:* The scope of the guidance has been changed 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 to limit the scope to the original in the 1987 guideline.

*Reason:* 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. Also the ICH Common Technical Document specifies requirements for description of analytical procedures in sections S.4.2 and P.5.2. The wider scope may lead to inconsistencies and redundancy.

#### **Lines 29-31, Scope**

*Suggestion:* The scope has been widened from NDAs and ANDAs to also cover BLAs and PLAs as well as supplements to all of the above. We supports this widening of the scope.

#### **Line 104, Types of analytical procedures**

*Suggestion:* Change "Regulatory analytical procedure" to "Pharmacopoeial tests".

*Reason:* This wording is consistent with Q6A.

#### **Lines 139-140, reference standards**

*Suggestion:* 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, reference standards**

*Suggestion:* 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, Reference standards**

*Suggestion:* 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, Methods Validation for INDs**

*Suggestion:* Add information from draft ICH Q7A 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" (section 19.80)

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

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

*Suggestion:* We suggest to change 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.

**Line 254, Sampling**

*Suggestion:* Add a reference to ISO5725, which gives guidance on number of samples.

*Reason:* Self-evident

**Line 311, Calculations**

*Suggestion:* Skip the word "order".

*Reason:* The word does not give meaning to the sentence

**Lines 313-346, Reporting of results**

*Suggestion:* Section J Reporting of results is suggested to be reduced to references to ICH Q3A(R – Drug Substances) and ICH Q3B(R – 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, Validation**

*Suggestion:* It is suggested that the entire section is 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, Robustness**

*Suggestion:* 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, Other Methods Validation Information**

*Suggestion:* 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 428-521, Validation in addition to ICH**

*Suggestion:* Replace the section by a reference to ICH Q2A & ICH Q2B

*Reason:* ICH Q2A and Q2B covers validation issues. Interpretations of other guidances and additions to these should be avoided. The fundamental concept of ICH is to offer harmonization between the three regions Japan, US and EU. In case areas covered by ICH should be provided with more details it should be suggested through ICH.

#### **Lines 431-438, Robustness**

*Suggestion:* Replace the section by a reference to ICH Q2B.

*Reason:* ICH Q2B covers robustness in section IX.

#### **Lines 395 & 439-454, Stress testing**

*Suggestion:* 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.

#### **Line 490-491, Drug Substance**

*Suggestion:* Change the wording to: The analytical procedure used should be capable of differentiating changes between past and present batches in case these affect product quality.

*Reason:* Only changes affecting the quality need to be detectable by the analytical procedures

#### **Lines 507-508, Peak identification**

*Suggestion:* 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”.

**Line 512-513, Drug Product**

*Suggestion:* Same suggestion and reason as for lines 490-491.

**Lines 522-546, Table on recommended validation characteristics**

*Suggestion:* Replace the section by a reference to ICH Q2A

*Reason:* Recommended validation characteristics is 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**

*Suggestion:* 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**

*Suggestion:* 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**

*Suggestion:* 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**

*Suggestion:* 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 covers specific tests.

**Lines 586-587, Verification of compendial methods**

*Suggestion:* 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 has been defined. We suggest that the specifics regarding verification is included in USP <1225>, which covers

validation of compendial methods. Also we suggest that the documentation for verification of compendial methods is not included in the submission.

*Reason:* This will help clarify FDAs current thinking regarding verification of compendial methods. The documentation for verification is of GMP relevance and should be reviewed by the agency upon request or during inspections.

**Line 599, Statistical Analysis**

*Suggestion:* delete "relative standard deviation" and replace with "analysis of variance".

*Reason:* 'relative standard deviation' is not a statistical analysis

**Lines 610-620, Comparative studies**

*Suggestion:* 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.

**Line 618, Comparative studies**

*Suggestion:* more batches should be represented in the comparative studies, representing the range of analysis.

*Reason:* self-evident.

**Lines 628-645, Revalidation**

*Suggestion:* 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 646-798, Methods Validation Package**

*Suggestion:* This is the bulk part of the document. The document should primarily be focused on this section as the requirements found here are not found elsewhere. Also this is the focus and content of the original 1987 version of the document.

*Reason:* Self explanatory.

**Lines 734-735, Shipment of samples**

*Suggestion:* 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 which may be voluminous, only parts relevant to the testing should be submitted.

#### **Lines 740-741, Storage of bulk substances**

*Suggestion:* 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**

*Suggestion:* 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

#### **Lines 1077-1079, Use of new instrumentation**

*Suggestion:* 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 utilized when appropriate" (ICH Q6B, section 2.1).

**Line 1237, References.**

*Suggestion:* the following references should be added:

- ISO 5725 Accuracy (trueness and precision) of measurement methods and results, part 1, 2, 3, 4 and 6.
- ISO 11095 Linear calibration using reference materials,
- Riley CM and Rosanske TW, Eds. Development and Validation of Analytical Methods. Elsevier 1996.
- Swartz ME and Krull IS. Analytical Method Development and Validation. Marcel Dekker 1997.
- Meier PC and Zünd RE. Statistical Methods in Analytical Chemistry, J Wiley 2000.

*Reason:* Self-explanatory.

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

*Suggestion:* Change the definition to that used in ICH Q6B.

*Reason:* Will harmonize the document with ICH document.

**Lines 1274-1275, Definition of Reagent**

*Suggestion:* Change the definition to that used in ICH Q6A.

*Reason:* Will harmonize the document with ICH document

**Lines 1277-1280, Definition of Specification**

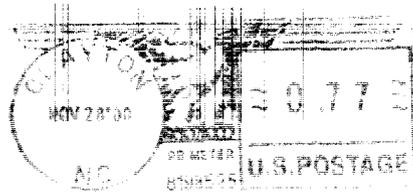
*Suggestion:* Change the definition to that used in ICH Q6A or ICH Q6B.

*Reason:* Will harmonize the document with ICH documents.

Kind regards



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Senior GMP Specialist



**FIRST CLASS**

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