



Date 10-October-2006

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Via fax and UPS

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



Re: Docket Nos. 2006D-0296 and 2006D-0297

International Conference on Harmonization; Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria; Annex on Residue on Ignition/ Sulphated Ash General Chapter and International Conference on Harmonization; Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciate the opportunity to comment on the above-referenced "International Conference on Harmonization draft guidances namely, "*Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria; Annex on Residue on Ignition/ Sulphated Ash General Chapter and Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria.*"

The draft guidances are intended to recognize the interchangeability between the local regional pharmacopoeias, thus avoiding redundant testing and different acceptance criteria in favor of a common testing strategy in each regulatory region and to facilitate regulatory acceptance of these proposed test methods and their interchangeability with test methods contained in the local regional pharmacopoeias.

GENERAL COMMENTS

1) Technical inter-changeability of monographs

This follows the PDG process stages (1 to 7)

The objective is to have monographs in EP, USP, and JP that are either identical ("same text") or fully equivalent

The strict implementation of ICH Q4B will require revision to the monographs as "harmonized" but not interchangeable

From an industry (implementation) perspective it is important that possible modifications of existing individual monographs (i.e. in EP, USP, or JP) do not result in inappropriate additional workload. For example, "uniformity of dosage units " to replace previous "uniformity of content" and "uniformity of mass", testing at end of shelf-life, etc.

2006D-0297

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GENERAL COMMENTS (continued)

2) Regulatory acceptance and regulatory implementation mechanisms

Industry objective is to have simple regulatory filing approaches, for instance a statement "complies with current EP / USP / JP"

Implementation of harmonized monographs should be for all products with a flexibility of implementation for old products.

For established products, the update of a general monograph may affect the finished product specifications; a recommendation by the Agency on how to interpret the new specifications should be included (for example, should the changes be reflected in the annual report?)

3) Pharmacopoeia updates

Pharmacopoeias have to be updated timely so that industry can reference the current (i.e. "harmonized") version

Further clarification for:

- Use and meaning of terminology, and related implications for industry, especially regarding "harmonized" with residual differences or attributes not harmonized vs. "interchangeable", "PDG proposal to Regulatory Acceptance" vs "non-PDG proposal"
- Implications for regulatory and technical implementation

Step 2 FDA (Q4B) Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria

<u>Paragraph, Section, Page*</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
<u>Title Page 1</u>	Title to be clearer The title of the guideline is not clear. Adding "Pharmacopoeia" to the title might help clarify the content.	Change: "Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria" Into: "Regulatory Acceptance of Pharmacopoeial Texts and inter-changeability"
<u>1.1 Objective(s) of the Guideline</u>	Is the objective of this guideline to facilitate the Regulatory acceptance of harmonized text by the FDA? The impact of ICH Q4B is difficult to ascertain since the harmonized monographs are only harmonized by attributes or have some residual differences. An explanation on how the residual differences will be managed versus the interchangeability may be needed. For established products:	Add: "Regulatory implementation of harmonized pharmacopoeial texts needs clarification. This ICHQ4B process enables FDA, EMEA and MHLW to describe recommendations to Marketing Authorization applicants."

	<p>The regulatory acceptance of harmonized texts is already an issue at the regional level. It may be too late to have the regulatory acceptance at this ICH stage (for example the uniformity of dosage units which needed a clarification by the EMEA and a postponement of implementation by the FDA)</p> <p>It would be useful to have the recommendation at the stage of the regional implementation.</p>	
<p><u>1.1 Objective(s) of the Guideline</u></p>	<p>Clarification: “For use in the three ICH regions”</p>	<p>Change: “for use in the three ICH regions”</p> <p>Into “for use in the three ICH regions (EU, US and JP)”</p>
<p><u>1.2 Background Last sentence of the 1st paragraph</u></p>	<p>Clarification: Explain EWG in text and add to glossary</p>	<p>Change: “EWG”</p> <p>Into “Expert Working Group”</p>
<p><u>1.2 Background 1st sentence of the 2nd paragraph</u></p>	<p>Completeness: Add in “Japanese” Ministry of Health, Labour and Welfare</p>	<p>Change: “Ministry of Health, Labour and Welfare”</p> <p>Into “Japanese Ministry of Health, Labour and Welfare”</p>
<p><u>1.3 Scope of the Guideline 2nd sentence</u></p>	<p>There is already flexibility in the system as Regulatory Authorities can choose to accept non-PDG text. Flexibility should stay at the level of the applicant.</p> <p>If the Agency is presented with additional flexibility, it may cause industry to manage several sets of specifications/methods for the same product according to the decision made by the country (acceptation/refusal of non-PDG text). It could lead to discrepancies between the countries/dossiers. It is not in line with harmonization and the process to facilitate RAAPAC.</p>	<p>Delete: “It also provides flexibility so that the Q4B EWG can evaluate, and regulatory authorities can choose to accept, non-PDG text”.</p>

<p><u>1.4</u> <u>General Principles</u></p>	<p>It should be noted that the regulatory impact has already been taken into consideration at the regional level.</p>	<p>Change: “The EWG will take scientific evaluations and regulatory impact into consideration when evaluating APAC”</p> <p>Into: “The EWG will take into consideration scientific evaluations and regulatory impact made at the regional level when evaluating APAC”</p>
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<p><u>2.3. Use of the Accepted APAC Page 4</u></p>	<p>In order to facilitate the interchangeability, the reference to the current JP, or Ph. Eur. or USP is sufficient.</p> <p>In order to limit the impact on already marketed products:</p> <ul style="list-style-type: none"> • this implementation should be mandatory only to new applications. • when the specifications already registered may be affected, some recommendation should be proposed by the Regulatory Authorities on how to establish the specifications in accordance with the new text in order to avoid the submission of variations. 	<p>Change: “APAC that have reached Step 5 can be used by stakeholders. When changing to the Step 5 APAC, any change notification and/or prior approval should be handled in accordance with established regional regulatory mechanisms. These regional mechanisms will be described in the topic-specific annexes.”</p> <p>Into: “APAC that has reached Step 5 is accepted and interchangeable. Applicants can use this APAC regardless of the reference to the Pharmacopoeia. The reference of this accepted APAC should be either current JP, or Ph. Eur. or USP.</p> <p>For established applications, in the topic-specific annexes</p> <ul style="list-style-type: none"> • It should be clearly mentioned that this implementation is not mandatory and no justification is required for not changing to the accepted APAC. • When changing to the accepted APAC, any change notification and/or prior approval should be handled in accordance with established regional regulatory mechanisms. These regional mechanisms will be clearly described with practical recommendations when the new description can affect the specifications already marketed.”
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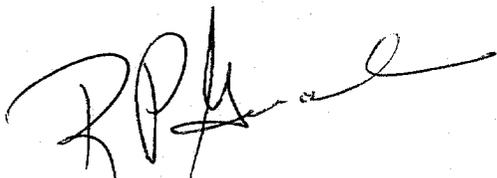
3. Glossary	Suggested terms to be added	Non-PDG text EWG
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Step 2 FDA (Q4B) Residue on Ignition/Sulphated Ash General Chapter Analytical procedures and/or Acceptance Criteria (APAC)

<u>Paragraph, Section, Page*</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
<u>#2 Q4B Outcome</u>	An additional paragraph, entitled "2.3 Statements, decisions and other information" should be added to include working practices for established applications.	Add: "2.3. Statements, decisions and other information: For established applications, this implementation is not mandatory and no justification is required for not changing to the accepted APAC. If implemented, the change should be handled in the US via the annual report
<u>#4 References 4.2 at the bottom of the page.</u>	Consistency: Since the JP monograph text is added as an attachment would it not be consistent to include the monograph test references from the EP and USP?	Add the (draft) text from the USP and EP for this Annex 1

On behalf of Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, we appreciate the opportunity to comment on the International Conference on Harmonization draft guidances *Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria; Annex on Residue on Ignition/ Sulfated Ash General Chapter* and *Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria* and are much obliged for your consideration.

Sincerely,



Richard Gural
 Vice President
 Regulatory Development

sanofi aventis

Because health matters

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FAX

Date: October 10, 2006

Number of pages including cover 6
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REMARKS:

Urgent

For your review

Reply ASAP

Please comment

Dear Sir/Madam:

Attached please find Sanofi-Aventis comments regarding:

International Conference on Harmonization; Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria; Annex on Residue on Ignition/ Sulphated Ash General Chapter and Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria.

This comment covers dockets 2006D-0296 and 2006D-0297. A hard copy will follow by courier.

Should you have any questions, please call me at your convenience.

Regards,

Linda Bowen