



Schering-Plough

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October 30, 2006

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

Re: **Docket No. 2006D-0297**
Docket No. 2006D-0296

**ICH Draft Guidance Q4B Regulatory Acceptance of Analytical Procedures
and/or Acceptance Criteria (RAAPAC)**

**ICH Draft Guidance Q4B Annex 1 to Regulatory Acceptance of Analytical
Procedures and/or Acceptance Criteria (RAAPAC) on Residue on
Ignition/Sulphated Ash General Chapter Analytical Procedures and/or
Acceptance Criteria**

Dear Sir/Madam:

Schering-Plough is fully supportive of the ICH Q4B Guideline and the respective Annex. We believe it is critical to have the endorsement of the regulators in the three regions in order for us to successfully implement harmonized pharmacopoeial chapters, procedures and acceptance criteria. Harmonization of pharmacopoeial procedures and acceptance criteria eliminates redundant and unnecessary testing, allowing our laboratories and those across the pharmaceutical industry to focus on more critical aspects of testing. However, the benefits of harmonization would not be realized without acceptance by the relevant regulatory authorities. Therefore, this is an important Guideline in order for us to fully implement the harmonized chapters and monographs. We offer the following comments on the subject draft Guideline and Annex for your consideration.

ICH Q4B Guideline

Title: We recommend not using the abbreviation of "RAAPAC" for the entire title of the Guideline as it dilutes the message of regulatory acceptance within the Guideline. The abbreviation of RAAPAC should be revised to "*regulatory acceptance of APAC*" throughout the Guideline. The partial abbreviation of "APAC" for Analytical Procedures and/or Acceptance Criteria is suitable and can be used throughout the Guideline without diminishing the overall intent.

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Line 11: We recommend that “EWG” be defined the first time it is used for those unfamiliar with the abbreviation.

Line 13: Please revise to “...the Ministry of Health, Labour and Welfare *in Japan*” to clarify the appropriate region similar to the European and United States regions.

Line 18: This paragraph explains the intended purpose of the Guideline and includes this statement, “...in favor of a common testing strategy in each regulatory region.” This does not adequately reflect the purpose of this Guideline as there already is a common strategy in each region, but not across regions. In addition, the Guideline does not only apply to testing, but also to acceptance criteria. For these reasons, we recommend revising the statement to “...in favor of a *common strategy across regions*.” We believe the intent of this Guideline is to support the application of the harmonized APAC throughout our laboratories regardless of where the laboratory is located. The advantage of a harmonized APAC is that our laboratories would be able to use the USP, or Ph. Eur., or JP to conduct the test and determine acceptance of the material, including compliance with any national or non-harmonized text required for the intended market. For example, it is envisioned that our laboratory in Europe would be able to conduct the Ph. Eur. Sulphated Ash test on a material to be released for the U.S. market. Similarly, it is envisioned that our laboratory in the U. S. would be able to conduct the USP Residue on Ignition test on a material to be released for the European market. In each case, the dossier would specify the pharmacopoeial chapter appropriate to that region yet the laboratory could utilize the harmonized chapter in their region to conduct the test, incorporating any necessary requirements for the release market as needed. Furthermore, the dossier should reflect the expectations of the Health Authority in that region and should not include any statement with regard to harmonization, unless the applicant intends to indicate something that is not aligned with the pharmacopoeia of that region. A dossier would not need to reflect compliance with all three pharmacopoeias as only one pharmacopoeia would be applicable in that region. Referencing more than the regional pharmacopoeia may imply that a material is tested and evaluated based on all three pharmacopoeias which would defeat the purpose of harmonization. Including only the regional pharmacopoeial reference in the dossier ensures that there is no misinterpretation as to what the applicant actually does versus what is expected by the Health Authority.

Line 19: Revise the sentence to make reference to ICH Q6A for the 11 General Chapters included in Attachment 1.

Line 29: Can you please clarify if pharmacopoeial guidance would also be covered under the scope? For example, the harmonized chapter on Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use is considered guidance or informational in the three pharmacopoeias. This chapter would also be included by reference in Attachment 1 under the general heading “Microbiological Quality”. Therefore, we believe this chapter is included in the scope but it is not clear that this type of guidance would be covered.

Line 37: This statement is extremely important to the process. To avoid duplication of effort, ICH Q4B should not discuss issues already deliberated and decided by the pharmacopoeias at the Pharmacopoeial Discussion Group.

Line 41: Is the APAC still “proposed” at this point, or is it considered official by the pharmacopoeia(s)? According to the process in section 2, EWG would evaluate the APAC as signed off by PDG. We recommend deleting this word to avoid confusion; sufficient detail is provided in section 2.

Line 47: Unilateral changes by a pharmacopoeia may be necessary to address issues for that region and may only affect monograph-specific issues. For example, it may be necessary to add a statement such as “unless otherwise indicated in the monograph”. In these cases, it should not void the final ICH status. The process should be flexible to allow for an assessment of any changes to see if there is any impact on the final ICH status.

Line 52: Revise to “The goal of Q4B”.

Line 54: Move the last sentence in the paragraph before the second sentence to improve clarity.

Line 59: Add the word “*submitted*” before “documents” to specify which documents are to be reviewed.

Line 71: Add to this step 5: “*which then facilitates inter-regional acceptance of the topic (Stage 7).*” Also the PDG stages should be revised accordingly to compensate for this new process.

Line 78: We recommend adding “*such as equivalency studies*” after other information. This is mentioned in Line 124 of the Attachment and would be helpful to the Q4B evaluation.

Line 80: This section of the Annex will be instrumental to industry in implementing the harmonized APAC and we highly encourage retention of this aspect in the Guideline. Implementation details may include timelines but may also include recommendations on how applicants are expected to implement certain APAC. For example, the information supplied by EMEA and EDQM on the Uniformity of Dosage Units and Microbiological Examination chapters respectively, may be useful to include in the Annex. Therefore the phrase “Statement or implementation timelines” may be better worded as “*Implementation statements or timelines*”.

Line 81: The statement of implementation would be more helpful at Stage 2 for consultation rather than at Stage 4. This is the aspect that will most impact industry.

Line 82: Before line 82, add another bullet to include the “APAC text”. This text was appropriately included in the attached Annex.

Line 82: Replace the word “methods” with “*analytical procedures*” to be consistent throughout the Guideline.

Line 85: This section (2.3) should be consistent with the description of the process in Attachment 2 and Figure 1. It currently implies that a harmonized APAC would need to reach Step 5 of the ICH Q4B process before it reaches Stage 6 of the PDG process. The process and the Figure would need to be aligned if this is the intent.

Line 85: Add to the end of the sentence “*and applied by regulators*”.

Line 86-87. We recommend clarifying “change notification and/or prior approval...with established regional regulatory mechanisms” to indicate that there may be no notification required to the Health Authority. The change to the dossier is dependent on the change and how it relates to the current information filed in the dossier. Therefore, it is conceivable that changing to a Step 5 APAC would not result in any change notification to and/or prior approval by the Health Authority. Also, as mentioned with Line 18, we do not anticipate a change in order to reference “ICH” or “harmonized” in the dossier as we believe it is unnecessary and may be misinterpreted.

Line 88: It may not be necessary to explain the regional mechanisms for handling changes as a result of ICH Q4B in the annexes as these may be explained in other regional guidance. We recommend adding “*if necessary*” to the end of the sentence.

Line 90: Please consider adding “*guidance*” to this definition for the reasons provided under Line 29 of the Scope.

Line 96: Use the term “*document submitter*” rather than “PDG”. If only one or two of the pharmacopoeias submit the documents through ICH Q4B, it would no longer be considered “PDG”.

Line 99: Please revise to “...the Ministry of Health, Labour and Welfare *in Japan*” to clarify the appropriate region similar to the European and United States regions.

Line 101: Remove the words “process produces an” as they are not necessary to convey the definition for the Outcome.

Line 121: We recommend this sentence to replace the current one for clarity: “A *commentary on any unresolved differences between one or more of the pharmacopoeias that may be an impediment to harmonisation.*”

Lines 123-125: We recommend presenting these in a different order which better represents the flow of information in the Briefing Note. Line 123 would become d., Line 124 would become b., and Line 125 would become c.

Line 123: Add to the end of the sentence: “Any specific issues relating to publication of the *official APAC, and*”

Line 141 (Figure 1, top left-hand box): The PDG Process Stage 5B is the “PDG Sign-off” stage which coincides with the “Document submission to Q4B”. We recommend including both in the box for Stage 5B.

Line 142 (Figure 1, arrow pointing left): The arrow from the Step 1 box to the PDG Process Stage 5B box does not reflect the process as explained in Attachment 2. The arrow should be from the Step 5 box (on the right) to the PDG Process Stage 6 box (on the left). Also, please refer to our comments for Line 85 to ensure the process is consistently explained throughout the Guideline.

ICH Q4B Annex 1

Introduction and Title: We recommend that RAAPAC be revised to “*regulatory acceptance of APAC*” throughout the Annex as explained in our comments to the Guideline Title.

Introduction, 2nd paragraph: Replace the word “output” with “*evaluation*” to better reflect the purpose of Q4B.

Section 2.1.1: We do not believe it is necessary to specify the sample size or the acceptance criteria in the dossier in many cases. This information may be specified in the monograph and need not be repeated in the dossier if the monograph is referenced in the dossier. If it is not specified in the monograph, then it would be appropriate to include this information in the dossier. We recommend adding to the end of this section: “*unless otherwise specified in the monograph*”.

Section 2.1.3 (new): A statement regarding acceptability of the grades of reagents, described in any of the three pharmacopoeias, that can be used for this procedure would be helpful (e.g., sulfuric acid which is used in this analytical procedure).

Section 3: It would be helpful if the implementation expectations could be included when the Annex is presented for comments at Step 2.

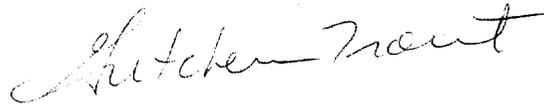
Section 4.1: It is not clear what is meant by the Note in this section which refers to the PDG cover letter, or what was changed in the cover letter based on Q4B comments.

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Section 4.2: Please include the chapter name and number within each reference. In addition, the USP information includes reference to the proposed as well as the official version whereas the JP and Ph. Eur. do not include a reference to the proposal. We do not believe it is necessary to include the reference to the proposals. However, if EWG thinks it is helpful to include these, then for consistency, the proposal references should be included for all three pharmacopoeias.

Schering-Plough appreciates the opportunity to comment on these draft guidances and we hope that you will take our comments under consideration.

Sincerely,

A handwritten signature in cursive script that reads "Gretchen Trout".

Gretchen Trout
Director, Regulatory Liaison and Policy
Global Regulatory Affairs