

October 10, 2006



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

RE: Docket No. 2006D-0297; International Conference on Harmonization; Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria

Merck & Co., Inc. is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck drug product candidates through developmental testing, clinical trials and licensure, Merck scientists address considerations influenced by this draft guidance describing the procedure to facilitate acceptance by regulatory authorities of harmonized pharmacopoeial test methods for the use in the three ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) regions (US, EU and Japan). We have extensive experience in the development and licensure of drug and biological candidates and concomitant development of analytical testing procedures; we have utilized those experiences to author the comments below.

General Comments

We commend the Food and Drug Administration (the Agency or FDA) for its commitment to global harmonization. We agree with the Agency's stated goal to avoid redundant testing and different acceptance criteria through the principles outlined in the draft guidance for industry: Q4B Regulatory Acceptance of Analytical Procedures and/or

[Docket No. 2006D-0297] International Conference on Harmonization; Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria

Acceptance Criteria (APAC); issued August 8, 2006 in Federal Register Docket No. 2006D-0297. This draft guidance establishes a process for the Q4B Quality Expert Working Group to evaluate harmonization proposals for specific APAC topics originating principally from the three-party Pharmacopoeial Discussion Group (PDG). Our comments are outlined in the following table (Attachment 1).

Specific Comments

In Attachment I, we tabulate our specific comments as follows: identification of the section (or paragraph) and line number in the draft guidance where the subject text is located, presentation of key comments with an explanation of our position, and suggested language for the proposed change. We support the development and adoption of this guidance as a necessary component to enable adoption and implementation of harmonized methods by regulatory authorities and the pharmaceutical industry. See Attachment 1 for more details.

We appreciate the opportunity to share our comments with respect to the International Conference on Harmonization; Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria. Please do not hesitate to contact me, should you have any questions.

Sincerely,



Taryn Rogalski-Salter, PhD
Director
US Regulatory Policy

Attachment enclosed

Attachment 1

Draft ICH Q4B Guidance on Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC) Step 2 – August 2006

Section, Line(s)	Comment with Explanation	Proposed change
Section 1.2 Background, Lines 14-15	<p><u>Text:</u> PDG is anticipated to be the principal source of APAC proposals to the Q4B EWG.</p> <p><u>Comment:</u> We recognize the practical reality expressed in this statement, but ask whether the process described in the Guidance could also be used to provide harmonized text completely separate from the compendia, as in a harmonization resulting strictly from text proposed by the regulatory agencies (FDA, EMEA, and MHLW). We would support such a generalization of the procedure.</p>	No changes are recommended to the text in this section, but we request consideration of a possible revision of the definition for “non-PDG text” in the Glossary to make the process even more general (see below).
Section 1.3 Scope of Guidance, Lines 28-29	<p><u>Text:</u> It also provides flexibility so that the Q4B EWG can evaluate, and regulatory authorities can choose to accept, non-PDG text.</p> <p><u>Comment:</u> Similar to the comment for Section 1.2 above, we support the flexibility of the Guidance to evaluate both PDG and non-PDG text, but suggest the Guidance could be further expanded by revising the definition of “non-PDG text”.</p>	No changes are recommended to the text in this section, but we request consideration of a possible revision of the definition for “non-PDG text” in the Glossary to make the process even more general (see below).
Section 1.4 General Principles, Lines 31-32	<p><u>Text:</u> The EWG will take scientific evaluations and regulatory impact into consideration when evaluating APAC.</p> <p><u>Comment:</u> We fully support the use of scientific evaluations and regulatory impact in the evaluation of all APAC.</p>	We support this statement and it should remain in the final Guidance.

<p>Section 1.4 General Principles, Lines 37-38</p>	<p><u>Text:</u> Interested parties are encouraged to focus their comments on the Q4B Outcome in the annex.</p> <p><u>Comment:</u> We agree that the focus on the Q4B Outcome in the annex is appropriate, since the detailed, technical evaluation should have occurred earlier during the PDG harmonization process.</p>	<p>We support this statement and it should remain in the final Guidance.</p>
<p>Section 1.4 General Principles, Line 39</p>	<p><u>Text:</u> Implementation details will be described in the topic-specific annexes...</p> <p><u>Comment:</u> We are concerned with the reference to “<u>Implementation details</u>” in the annexes as this suggests the possibility of including requirements that are specific to the regulatory update process. As such, we do not support this wording, but suggest alternative wording that is more consistent with the focus elsewhere in the Guidance on <u>timing</u> for implementation. (See section 2.2 Annex Contents.)</p>	<p><u>Revised Text:</u> <u>Details on timing for implementation</u> will be described in the topic-specific annexes...</p>
<p>Section 1.4 General Principles, Lines 39-40</p>	<p><u>Text:</u> ...the topic-specific annexes which will be available on the ICH website.</p> <p><u>Comment:</u> We support the availability of the annexes on the ICH website to ensure knowledge by all impacted stakeholders (including regulatory agencies, the compendia, and industry) of the specific harmonized text that may be implemented.</p>	<p>We support this statement and it should remain in the final Guidance.</p>
<p>Section 1.4 General Principles, Lines 42-44</p>	<p><u>Text:</u> In order to preserve transparency, once the EWG has made a recommendation, any subsequent revisions to the PDG harmonized text should occur only through the PDG process.</p> <p><u>Comment:</u> We consider it essential that subsequent revision to PDG harmonized text should occur only through the PDG process. (But see also our concern with the potential impact of unilateral changes made by the compendia in our comment</p>	<p>We support this statement and it should remain in the final Guidance</p>

	below.)	
Section 1.4 General Principles, Lines 47-48	<p><u>Text:</u> Unilateral changes/revisions by any of the individual pharmacopoeias will void the ICH final status.</p> <p><u>Comment:</u> We have serious concerns with this statement, and find it requires the most critical revision to the draft Guidance. While we recognize the possibility of unilateral action by individual compendia regarding harmonized text, we believe such action should not result in an automatic “void” of the ICH final status, as this will undoubtedly create significant uncertainty as to how to proceed from both a regulatory and quality perspective, and could jeopardize the availability of some drug products until such time as clarification can be provided. We believe that some unilateral actions by compendia have no practical impact on interchangeability, so that a re-assessment by Q4B EWG would be important to determine whether the Outcome is actually affected. Furthermore, given the intended flexibility of the Q4B process, it is reasonable that the Q4B EWG could re-consider the text as “non-PDG text” after such a unilateral change by one of the compendia, with a possible re-statement of the current acceptability of the APAC by the regulatory authorities. We believe this maintains the intent of the Q4B process which is to enable implementation of harmonized text, despite differences that may exist between the individual compendial texts. A recommendation for revised text is provided.</p>	<p><u>Revised Text:</u> Unilateral changes/revisions by any of the individual pharmacopoeias <u>will result in a re-assessment by the Q4B EWG to determine whether the changes/revisions have any practical impact on the previously determined acceptance of the APAC as described in the topic-specific annex. If it is determined that there is no impact resulting from the changes/revisions, then the annex will be updated to reflect the revised compendial version, with no change indicated to the Q4B Outcome. If, on the other hand, it is determined that the unilateral changes/revisions made by the individual pharmacopoeia do in fact impact the Outcome, then consideration will be given by the Q4B EWG to re-classify the APAC as non-PDG text, with the possible re-statement of the Outcome, but removing reference to the revised compendial text. In rare instances, after other options have been pursued, it may be necessary to void the ICH final status as a result of unilateral compendial revisions. In such instances, guidance will be provided by the Q4B EWG through the annex to try and minimize the impact resulting from the voided status, until a satisfactory resolution can be achieved.</u></p>
Section 2 GUIDANCES Lines 50-71	<p><u>Text:</u> (Section 2. GUIDANCES, Sub-sections 2.1, 2.1.1, 2.1.2, 2.1.3, 2.1.4, 2.1.5).</p> <p><u>Comment:</u> We are in agreement with these sections of the Guidance.</p>	<p>We support these sections and they should remain unchanged in the final Guidance.</p>

<p>Section 2.2 Annex Contents, Line 73</p>	<p><u>Text:</u> The topic-specific annexes will contain the following information...</p> <p><u>Comment:</u> Overall, we agree with Section 2.2 Annex Contents and consider the details provided in this section to be helpful.</p> <p><u>Note:</u> Four specific comments about this Section are provided below.</p>	<p>We support this section and it should remain in the final Guidance. Please consider the following four specific comments about the details of this Section.</p>
<p>Section 2.2 Annex Contents, Lines 78-79</p>	<p><u>Text:</u> As appropriate, statements, decisions and other information that will assist in the use of the accepted APAC by stakeholders</p> <p><u>Comment:</u> We support the annex containing information that will assist in the use of the APAC, but we have concern about the possible inclusion of implementation details that may create specific requirements related to the regulatory update process.</p>	<p>We support the inclusion of information that will assist in the use of APAC by stakeholders, and this statement should remain in the final Guidance. But we request that the Q4B EWG not include requirements within this section of the topic-specific annexes that are related to the regulatory update process.</p>
<p>Section 2.2 Annex Contents, Lines 80-81</p>	<p><u>Text:</u> Statement or implementation timelines indicating regulators' advice on when stakeholders can begin using the APAC <u>(at Step 4)</u>.</p> <p><u>Comment:</u> We support the annex containing regulator's advice on when to begin using the APAC as this is critical for implementation planning. We also agree that this implementation detail should focus exclusively on the timing aspect of "<u>when</u> stakeholders can begin using the APAC. " (See also previous comment on <u>Section 1.4 General Principles, Line 39</u>). And we agree that it is appropriate to add the implementation timeline at Step 4 of the Q4B process. But the wording in the Guidance is not quite clear and suggests a possible typographical error (placement of the word "<u>or</u>"). Further, the inclusion and placement of the parenthetical "<u>(at Step 4)</u>" seems confusing as it may imply that stakeholders may begin using the APAC at Step 4 of the process, which is clearly not the intent.</p>	<p><u>Revised Text:</u> Statement <u>of</u> implementation timelines indicating regulators' advice on when stakeholders can begin using the APAC <u>(added to Annex at Step 4)</u></p> <p><u>OR:</u> Statement <u>or clarification of</u> implementation timelines indicating regulators' advice on when stakeholders can begin using the APAC <u>(added to Annex at Step 4)</u></p>

<p>Section 2.2 Annex Contents Line 124</p>	<p><u>Text:</u> (Not currently included in Guidance.)</p> <p><u>Comment:</u> Attachment II to the Guidance (PDG Document Submission Provided for ICH Q4B EWG Evaluation) includes text and information that is to be provided in the “document submission” to the Q4B EWG. Among the supporting information in Attachment II is listed: “If any equivalency study was conducted, a summary of the outcome.” We request inclusion of this same information in the Annex Contents as listed in Section 2.2 of the Guidance, since knowledge of whether an equivalency study was performed and the outcome of the study would be extremely valuable information for stakeholders using APAC.</p>	<p><u>Insert Text:</u> (underlined)</p> <p>The topic-specific annexes will contain the following information. Other information might be incorporated on a case-by-case basis.</p> <ul style="list-style-type: none"> • Topic title • Introduction • Q4B Outcome • <u>A statement indicating whether any equivalency study was conducted, and a summary of the outcome</u> • As appropriate, statements, decisions and other information that will assist in the use of the accepted APAC by stakeholders • Statement <u>of</u> implementation timelines indicating regulators' advice on when stakeholders can begin using the APAC <u>(added to Annex at Step 4)</u> • References to methods and acceptance criteria, as appropriate.
<p>Section 2.2 Annex Contents</p>	<p><u>Text:</u> (Not currently included in Guidance.)</p> <p><u>Comment:</u> We note that the topic-specific Annex on Residue on Ignition/Sulphated Ash, provided for review in conjunction with this review of this Q4B draft Guidance, includes the full Japanese Pharmacopoeia text for this test to reflect the specific document that was evaluated by the Q4B EWG. In our comments on the Annex, we expressed appreciation and support for inclusion of the specific harmonized text. The clarity and consistency provided by publication of one appropriate, specific text in the Annexes is a critical aspect that will contribute to successful application of standardized, harmonized APAC. We further note that Section 2.2 of the</p>	<p><u>Insert Text at the end of Section 2.2 Annex Contents:</u> (underlined)</p> <p><u>The specific harmonized APAC text that was evaluated by the Q4B EWG.</u></p>

	<p>Guidance does not specifically include the APAC text evaluated by the Q4B EWG among the Annex Contents. We believe this should be corrected in the Guidance by addition of the proposed text as indicated.</p>	
<p>Section 2.3 Use of the Accepted APAC, Lines 85-88</p>	<p>Text: 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>Comment: At its core, the Q4B process is an evaluation by the regulatory agencies whereby an allowance to use the APAC is granted. As described in the Guidance, the process concludes with the ability to use accepted APAC once they reach Step 5. This is captured in the first sentence of Section 2.3 and should be a sufficient conclusion for the process. We are concerned by the additional two sentences in this Section and we disagree with some of the specific language. We recognize that “changing to the Step 5 APAC...should be handled in accordance with” appropriate regulatory mechanisms. But the necessary action may depend on a variety of factors which may vary depending on the particular company, country, product, and APAC, including how the specific information is currently filed and the significance of the actual change resulting from adoption of the APAC. We are particularly concerned with the final sentence: “These regional mechanisms will be described in the topic-specific annexes.” The last two sentences in this Section address the regulatory filing process, and as we have previously stated, we do not believe it is necessary or appropriate to include requirements for the regulatory filing process – especially “change notification and/or prior approval” – in either the Guidance or the Annexes. Given our concerns, we recommend revising the text in this Section as indicated in the column to the right, eliminating all but the first sentence.</p>	<p>Text: 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>Section 3 Glossary, Lines 95-96</p>	<p><u>Text:</u> <i>Non-PDG</i> – One or two of the regional pharmacopoeias, but not all 3 pharmacopoeias acting together as the PDG.</p> <p><u>Comment:</u> We realize one of the practical outcomes of the Q4B process is to enable agreement by regulators in the event PDG can not reach agreement, and we fully support this aspect of the Q4B Guidance. But we ask whether consideration has been given to the possibility of an equally helpful harmonized document that may originate totally outside of the compendia or PDG (e.g. a document originating from the regulatory agencies themselves). An expansion of the definition of “non-PDG” would provide such an allowance in the Guidance.</p>	<p><u>Revised Text:</u> <i>Non-PDG</i> – One or two of the regional pharmacopoeias, but not all 3 pharmacopoeias acting together as the PDG. <u>This term may also apply to text originating from non-pharmacopoeial or PDG sources.</u></p>
<p>Attachment II, Line 113</p>	<p><u>Text:</u> Attachment II PDG Document Submission Provided for ICH Q4B EWG Evaluation</p> <p><u>Comment:</u> We agree with and support the information included in this Attachment to the Guidance. However, the process described is specific to “PDG text“, as indicated in bold, and a note should be added to indicate a similar process for “non-PDG text”.</p>	<p>We support this Attachment and it should remain in the final Guidance, with the following addition.</p> <p><u>Additional Text:</u> <u>Non-PDG Document Submission: A process that is generally consistent with that detailed for PDG Document Submission may be followed for non-PDG text.</u></p>
<p>Attachment II, Lines 125-126</p>	<p><u>Text:</u> The projected publication schedule in each pharmacopoeia, with clear indication as to the anticipated final PDG Stage 7 implementation date</p> <p><u>Comment:</u> It is our understanding that the interpretation of Stages 6 and 7 in the PDG Working Procedure may be changed to incorporate the Q4B process. (Other changes in interpretation of the PDG Stages have previously occurred.) If this change occurs, reference to PDG Stage 7 (or Stage 6A, 6B, or new Stage 6C) may result in an inaccuracy in the Q4B Guidance. It is recommended to remove the specific reference to the PDG Stage and leave only the text related to implementation date.</p>	<p><u>Revised Text:</u> The projected publication schedule in each pharmacopoeia, with clear indication as to the anticipated final <u>implementation date</u></p>

<p>Figure I, Lines 138-147</p>	<p><u>Text:</u> Figure I – Topic-Specific Annex Process</p> <p><u>Comment (1):</u> This figure is helpful in showing the parallel processes for PDG and Q4B and we support its inclusion in the Guidance. However, similar to our comments on Attachment II, the figure is specific to the PDG initiated process and allowance should be made for “non-PDG text”.</p> <p><u>Comment (2):</u> We would draw your attention to the inclusion in the PDG Process boxes of references to Stage 6 and Stage 7. In light of our previous comment on Attachment II, we suggest consideration of text that may not be impacted by possible changes in the interpretation of PDG Stage 6 and 7. We note that the PDG Process Stage 6 box in Figure I is labeled “Regional pharmacopoeial implementation“, while Stage 6 in the current USP29 chapter <1196> <u>Pharmacopoeial Harmonization</u> is labeled: “Regional Adoption and Implementation”. And the PDG Process Stage 7 box is labeled “Inter-regional Acceptance“, which is consistent with the proposed new PDG interpretation for Stage 7, but not consistent with the current USP29 label: “Inter-regional Implementation”.</p>	<p><u>Revised Text (1):</u> We support inclusion of Figure I but recommend revision of the Figure to indicate submission of non-PDG text. This can be accomplished most simply by adding a new box – to the right of the Q4B process column – labeled “Non-PDG Process” with arrows connecting this new box to the top box “Step 1” of the Q4B process. This has the advantage of visually reinforcing the central role played by the Q4B process for both PDG and non-PDG text, which is the focus of the overall Guidance. Alternatively, but not as desirable, is the possible addition of a new Figure II to show the “Non-PDG Process”, but this would share the entire Q4B portion of the process from Figure I.</p> <p><u>Revised Text (2):</u> Consider use of text for the PDG Process Stage 6 and PDG Process Stage 7 boxes in Figure I that will not be impacted by possible changes in the interpretation of these stages.</p>