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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RE: Docket No. 2006D-0296; International Conference on Harmonization; Draft Guidance on Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria; Annex on Residue on Ignition/Sulphated Ash General Chapter

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 proposed testing annex describing the harmonized pharmacopoeial test method for residue on ignition/sulphated ash. 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stated goal to avoid redundant testing and different acceptance criteria through the principles outlined in the draft guidance for industry: Q4B Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (August 8, 2006. Docket No. 2006D-0297). The subject of this comment letter, Annex 1: Residue on Ignition/Sulphated Ash General Chapter, provides a

draft document at Step 2 of the ICH (International Conference on Harmonization) process which describes the harmonized test method for this assay. 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 page 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 have one significant comment concerning the section on "*appropriate sample weight*". We do not support inclusion of sample weight in this Annex. This weight should be defined by the sponsor during method development or in a specific compendial monograph. 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; Annex on Residue on Ignition/Sulphated Ash General Chapter. 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 Annex on Residue on Ignition/Sulphated Ash
Step 2 – August 2006

Section, Page	Comment with Explanation	Proposed change
Section 2.1.1, Page 2	**Text**: Unless otherwise specified, an appropriate sample weight is chosen, typically 1-2 g, to result in a level of residue sufficient to be accurately measurable by weight (typically 1 mg). The sample size and the acceptance criteria should be specified in the application dossier. **Comments**: We are concerned with the inclusion of typical sample weight and residue weight in the first sentence of this section. While we agree that it is important that a suitable sample size be used for the test, we believe that reference to typical weights is an unnecessary detail in the Annex. The appropriate sample weight will either be stated in a specific compendial monograph, or demonstrated during method development and/or validation. It should also be recognized that the appropriate sample weight may be tied to the acceptance criteria for the specific material undergoing testing, so a statement of typical weights may result in decreased – rather than increased – clarity and usability of the Annex. We recommend removal of the reference to typical weights in this section of the Annex. And we have serious concern with the requirement to specify the sample size in the application dossier, as stated in the second sentence of this section. As indicated above, for materials with a compendial monograph, the appropriate sample amount for the Residue on Ignition/Sulphated Ash test will already be stated in the monograph, so inclusion of the	**Revised Text:** Unless otherwise specified, an appropriate sample weight is chosen~~, typically 1-2 g,~~ to result in a level of residue sufficient to be accurately measurable by weight.~~ (typically 1 mg).~~ The appropriate sample weight should either be stated in a compendial monograph, or demonstrated during method development and/or validation. The ~~sample size and the~~ acceptance criteria should be specified in the application dossier, only if not otherwise available in a compendial monograph.

Section, Page	Comment with Explanation	Proposed change
	sample amount in the dossier becomes redundant. For materials that do not have a compendial monograph, it is expected that the suitability of the sample amount used in the Residue on Ignition/ Sulphated Ash test would be demonstrated during method development and/or validation. With this understanding, we believe that inclusion of the sample weight in the application dossier is an inappropriate and unnecessary requirement. Based on our concerns, we recommend revision of the text to remove the requirement to specify the sample size in the dossier, as indicated in the column to the right. We further recommend addition of a sentence to reflect that the appropriate sample weight should either be stated in a compendial monograph, or demonstrated during method development and/or validation. On the other hand, we do agree that the acceptance criteria for the test should be included in the application dossier, but only if not otherwise provided in a specific compendial monograph for the material. We have provided a suggestion for revised text in the column labeled "Proposed Change". We believe revision of the text as indicated will still provide sufficient information to users of the Annex and to regulatory agencies to ensure that appropriate sample size and acceptance criteria are used for the test.	
Section 2.1.2, Page 2	**Text:** Regional GMP requirements cover calibration of the muffle furnace. **Comment:** We have some concern with reference to "regional" GMP requirements in light of the global nature of today's pharmaceutical industry and the emphasis on	**Revised Text:** ~~Regional GMP requirements cover calibration of the muffle furnace.~~ The muffle furnace should be appropriately calibrated to ensure compliance with GMP requirements.

Section, Page	Comment with Explanation	Proposed change
	harmonization. We also believe this section is not worded clearly to indicate the need to ensure calibration of the muffle furnace used in the test. We have provided revised text for your consideration.	
Section 2.1.3 (new), Page 2	**Text:** (Not currently included in Annex.) **Comment:** While we agree with the Q4B Outcome that the referenced texts are acceptable in the three ICH regions, there is an additional, often-overlooked detail that needs to be addressed to enable performance of a single test for Residue on Ignition/Sulphated Ash. The grades of sulfuric acid required by the USP, Ph. Eur., and JP for use in the test are not necessarily identical. However, we consider this to be of no practical consequence, and advocate that the use of any appropriate grade of sulfuric acid according to the requirements of any of the pharmacopoeias should be suitable for the test. This is summarized in our proposed text for new Section 2.1.3 in the column to the right.	**Additional Text:** 2.1.3 Any suitable grade of sulfuric acid, as defined by any of the pharmacopoeias (JP, Ph. Eur., or USP), is acceptable for use in the test.
Section 3, Page 2	**Text:** Implementation **Comment:** Consistent with our comments on the Q4B Draft Guidance for Industry (August 8, 2006. Docket 2006D-0297), the Annex should contain information on the timing for implementation. The Annex should not contain additional implementation details, especially those that may be related to the process for regulatory updates. We request clarification by a change to the title of this section to indicate the section describes the implementation timing.	**Revised Text:** 3. Implementation Timing
Section 4.2, Page 2	**Text:** United States Pharmacopeia (USP): Pharmacopeial Forum, Volume 31, Number 5, September 2005 and official in	United States Pharmacopeia (USP): Pharmacopeial Forum, Volume 31, Number 5, September 2005 and official in USP 29, 2nd Supplement,

Section, Page	Comment with Explanation	Proposed change
	USP 29, 2nd Supplement, August 2006 **Comment:** We recommend addition of the reference to USP chapter <281> Residue on Ignition for consistency with the specific chapter/monograph references included for JP and Ph. Eur in this section of the Annex.	August 2006 (reference <281> Residue on Ignition)
Page 3	**Text:** JPXV Text **Comment:** We appreciate the inclusion of the full JP text for the Residue on Ignition/ Sulphated Ash method, since differences in the specific text adopted by the different pharmacopoeias has created much of the confusion surrounding "harmonized" text coming from the PDG process. The clarity and consistency provided by publication of one appropriate, specific text in this – and other – Annexes is a critical aspect that will contribute to successful application of standardized, harmonized APAC.	No changes are recommended to the text in this section**.**
Paragraph 4 Page 3	**Text:** Take the amount of test sample specified in the individual monograph… **Comment:** The inclusion of the statement above in the harmonized text further supports our comments on Section 2.1.1 that sample size should not need to be specified in the dossier. The sample amount will either be available in the appropriate compendial monograph, or will have been demonstrated to be suitable for a non-compendial material. It may be also noted that inclusion of the sample amount in the dossier creates the potential for a conflict between compendial requirements and regulatory commitment. If the sample amount is specified in the compendial monograph and also in	No changes are recommended to the text in this section**.**

Section, Page	Comment with Explanation	Proposed change
	the application dossier, and the sample amount in the monograph is subsequently changed (which could occur without impact to the harmonized text on Residue on Ignition/ Sulphated Ash), different sample amounts would be required from a compendial and regulatory perspective. We feel this is an unnecessary complication which can be avoided by deleting the requirement to include sample weight in the application dossier, as we have previously commented on Section 2.1.1 of the Annex.	
Paragraph 4 Page 3 (Also referenced in Paragraph 1 and 5)	**Text**: Moisten the sample with a small amount (usually 1 mL) of sulfuric acid… **Comment:** One difference that remains with the harmonized text for Residue on Ignition/ Sulphated Ash concerns the grade of sulfuric acid that is to be used in the test. We believe that the use of any appropriate grade of sulfuric acid should be allowed as defined by any of the three pharmacopoeias. This allowance for the use of any suitable grade of sulfuric acid in the harmonized method can be accomplished by addition of the proposed (new) text to Section 2.1.3 of the Annex, as we recommended previously herein.	No changes are recommended to the text in this section.