European Medicines Agency

June 2006
EMEA/CHMP/ICH/222063/2006

ICH Topic Q 4 B Annex
Annex to Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC)

Step 3

ANNEX TO NOTE FOR GUIDANCE ON REGULATORY ACCEPTANCE OF ANALYTICAL PROCEDURES AND/OR ACCEPTANCE CRITERIA (RAAPAC)

(EMEA/CHMP/ICH/222063/2006)

TRANSMISSION TO CHMP	June 2006
TRANSMISSION TO INTERESTED PARTIES	June 2006
DEADLINE FOR COMMENTS	December 2006

Note: This Annexe to the *ICH Q4B Guideline* has been developed by the ICH Q4B Expert Working Group and is being presented for consultation by the regulatory parties, in accordance with the ICH Process. On reaching Step 4 of the Process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 85 75 Fax (44-20) 75 23 70 40
E-mail: mail@emea.eu.int http://www.emea.eu.int

Having achieved Step 3 of the ICH Process at the ICH Steering Committee meeting on June 8, 2006, this Annexe to the ICH Q4B Guideline is being presented for consultation by the regulatory parties.

1. Introduction

The ICH Q4B Guideline describes a process to facilitate the three ICH-region Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC).

This topic-specific annexe is the output of the Q4B Step 2 process for residue on ignition/sulphated ash and will be added to the guideline after Step 4. The APAC was submitted by PDG.

2. Q4B Outcome

2.1 Analytical Procedures
The Q4B EWG concludes that the referenced texts are considered to be acceptable in the three ICH regions given the following:

2.1.1 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.
2.1.2 Regional GMP requirements cover calibration of the muffle furnace.

2.2 Acceptance Criteria
The APAC evaluated did not contain acceptance criteria.

3. Implementation

Will be provided at Step 4 of the annexe

4. References

4.1 The PDG Stage 5B sign-off document: Japanese Pharmacopoeial Forum Volume 14, Number 4 (December 2005). (Note: the PDG cover letter published in this volume was changed based on Q4B comments.)

4.2 The pharmacopoeial references for residue on ignition/sulphated ash as of Step 2 for this annexe:

Japanese Pharmacopoeia (JP): draft text as provided to Q4B, attached. JPXV in Japanese was published in March, 2006 and implemented in April, 2006 (2.44 Residue on Ignition/Sulphated Ash). English version will be published later.
European Pharmacopoeia (Ph. Eur.) Supplement 5.3 (official on January 2006) (reference 01/2006:20414)
United States Pharmacopeia (USP): Pharmacopeial Forum, Volume 31, Number 5, September 2005 and official in USP 29, 2nd Supplement, August 2006

JPXV Text

(JP XV in Japanese - Publication: March, 2006, Implementation: April, 2006)

The Residue on Ignition/ Sulphated Ash Test is a method to measure the amount of residual substance not volatilized from a sample when the sample is ignited in the presence of sulfuric acid according to the procedure described below. This test is usually used for determining the content of inorganic impurities in an organic substance.

The description, for example, “not more than 0.1% (1g)”, in a monograph, indicates that the mass of the residue is not more than 1mg per 1g of the substance in the test in which about 1g of the substance is weighed accurately and ignited by the procedure described below, and “after drying” indicates that the sample is tested after being dried under the conditions specified in the test for Loss on drying.

Ignite a suitable crucible (for example, silica, platinum, quartz or porcelain) at 600 ± 50ºC for 30 minutes, cool the crucible in a desiccator (silica gel or other suitable desiccant) and weigh it accurately.

Take the amount of test sample specified in the individual monograph in the crucible and weigh the crucible accurately. Moisten the sample with a small amount (usually 1 mL) of sulfuric acid, then heat gently at a temperature as low as practicable until the sample is thoroughly charred. After cooling, moisten the residue with a small amount (usually 1 mL) of sulfuric acid, heat gently until white fumes are no longer evolved, and ignite at 600 ± 50ºC until the residue is completely incinerated. Ensure that flames are not produced at any time during the procedure. Cool the crucible in a desiccator (silica gel or other suitable desiccant), weigh accurately and calculate the percentage of residue.

Unless otherwise specified, if the amount of the residue so obtained exceeds the limit specified in the individual monograph, repeat the moistening with sulfuric acid, heating and ignition as before, using a 30-minute ignition period, until two consecutive weighings of the residue do not differ by more than 0.5 mg or until the percentage of residue complies with the limit in the individual monograph.