

COMMENTS CONCERNING SOME REVISED/CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 6.7

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the March 2009 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

GENERAL TEXTS

1. General Notices

Following the creation of the new general chapter 5.1.8. *Microbiological quality of herbal medicinal products for oral use*, a definition for 'herbal medicinal product' has been added. The definition is based on Directive 2001/83/EC of the European Parliament and of the Council of the European Union.

2.4.14. Sulphated ash

This chapter has been revised to indicate its status within the context of pharmacopoeial harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*. For information, this chapter is now interchangeable in the ICH regions (Q4B Annex 1: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Residue on Ignition/Sulphated Ash General Chapter).

2.6.12. Microbiological examination of non-sterile products: microbial enumeration tests

This chapter has been revised to indicate its status within the context of pharmacopoeial harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*. For information, this chapter is now interchangeable in the ICH regions (Q4B Annex 4A: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests General Chapter).

2.6.13. Microbiological examination of non-sterile products: test for specified micro-organisms

This chapter has been revised to indicate its status within the context of pharmacopoeial harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*. For information, this chapter is now interchangeable in the ICH regions (Q4B Annex 4B: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-sterile Products: Tests for Specified Micro-organisms General Chapter).

2.6.31. Microbiological examination of herbal medicinal products for oral use

The semi-quantitative test for *E. coli* (probable number method) is the same as that currently described in the

Appendix (special Ph. Eur. provision) to the harmonised chapter 5.1.4. Since herbal drugs are outside the scope of pharmacopoeial harmonisation this test has been transferred into the present chapter.

The absence test for *E. coli* and the semi-quantitative test for bile-tolerant gram-negative bacteria (probable number method) are the same methods as the ones currently published in the harmonised chapter 2.6.13. It is proposed also to describe them in the present chapter. The proposed method for *Salmonella* (test for absence) is similar to the method currently published in chapter 2.6.13 but the proposed method has been adapted to the increased sample size (25 g or 25 ml instead of 10 g or 10 ml), shown to be appropriate for herbal medicinal products. For herbal medicinal products with naturally high bioburden the use of buffered peptone medium instead of casein soya bean digest broth is reasonable because of higher buffer capacity.

2.9.17. Test for extractable volume of parenteral preparations

This chapter has been revised to indicate its status within the context of pharmacopoeial harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*. For information, this chapter is now interchangeable in the ICH regions (Q4B Annex 2: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Extractable Volume of Parenteral Preparations General Chapter).

5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use

The special Ph. Eur. provision for microbiological quality of herbal medicinal products for oral use has been deleted since it is now dealt with in the newly created chapter 5.1.8. A sentence at the end of the document refers to this chapter.

Furthermore, this chapter has been revised to indicate its status within the context of pharmacopoeial harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*. For information, this chapter is now interchangeable in the ICH regions (Q4B Annex 4C: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter).

5.1.8. Microbiological quality of herbal medicinal products for oral use

General chapter 5.1.4 contains recommendations for herbal medicinal products (at the end of Table 5.1.4.-1 Special Ph. Eur. provision).

It has been reported on different occasions that these recommendations are impractical for many herbal drugs (EDQM Symposia: Herbal Medicinal Products: Quality Evaluation, Nice, November 2000; Microbiological Control Methods in the European Pharmacopoeia, Copenhagen, May 2003).

The matter has been discussed in the group of experts in charge of microbiology and herbal drugs and in order to deal fully with the issues it appeared necessary to create a specific working party with both microbiologists and herbals specialists. Their proposals are included in the following text.

Maximum acceptable count. The factor 5, previously used to calculate the maximum acceptable count from the acceptance criterion, has been maintained in this chapter to take account of the variability of the methods.

Categories. As the categories currently used in chapter 5.1.4 lead to divergent interpretations from one country to another, revision of the categories is proposed as follows:

- Category A: encompasses medicinal products containing herbal drugs, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (for example, herbal teas, with or without added flavourings);
- Category B: encompasses medicinal products containing, for example, extracts and/or herbal drugs,

with or without excipients, where the method of processing (for example, extraction) or, in the case of herbal drugs, of pre-treatment (for example, with water vapour) reduces the levels of organisms to below those stated for this Category;

- Category C: encompasses medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where the method of processing (for example, extraction with low-strength ethanol or water that is not boiling, or low temperature concentration) or, in the case of herbal drugs, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required by Category B. Furthermore, the limit for *E. coli* in Category A products and for bile-tolerant gram-negative bacteria in Category C products has been relaxed.

It should be noted that in the acceptance criteria for *Salmonella* the sample size has been increased to 25 g or 25 ml.

If this text is accepted, references to herbal medicinal products will be deleted from the special Ph. Eur. provision in chapter 5.1.4. It should be noted that the special Ph. Eur. provision in chapter 5.1.4 would still cover oral dosage forms containing raw materials of animal or mineral origin.

5.8. Pharmacopoeial Harmonisation

This chapter has been revised within the framework of pharmacopoeial harmonisation. General chapters 2.4.14, 2.6.12, 2.6.13, 2.9.17 and 5.1.4 have been added.

DOSAGE FORMS

Glossary (1502)

Definitions of a number of dosage forms are indicated to facilitate the comprehension of the monographs and general chapters.

Semi-solid preparations for cutaneous application (0132)

Uniformity of dosage units: the monograph was recently revised to add a test for uniformity of dosage units for

preparations supplied in single-dose containers; the scope of the test is now expanded to include preparations supplied in metered-dose containers.

Cutaneous patches: a section is added for these dosage forms, which have been developed recently (using for example the analgesic effect of capsaicin) and are manufactured in a similar way to transdermal patches.

VACCINES FOR HUMAN USE

Measles, mumps and rubella vaccine (live) (1057)

Labelling: the pregnancy caution statement has been deleted; safety statements are considered to be part of the Summary of Product Characteristics recommendations and therefore not to belong to a Pharmacopoeia monograph.

Poliomyelitis vaccine (inactivated) (0214)

Protein nitrogen content: to remove ambiguity, the word 'nitrogen' has been deleted since the test determines a protein content; in addition, a statement has been added in the production section to give the possibility to omit

the test on the final lot if performed with satisfactory results on the purified monovalent harvests or on the inactivated monovalent harvests.

Rubella vaccine (live) (0162)

Varicella vaccine (live) (0648)

Labelling: the pregnancy caution statement has been deleted; safety statements are considered to be part of the Summary of Product Characteristics recommendations and therefore not to belong to a Pharmacopoeia monograph.

HOMEOPATHIC PREPARATIONS

Homoeopathic preparations (1038)

The monograph has been modified to exempt homoeopathic preparations from the test for uniformity

of dosage units under the same conditions as the test for uniformity of content.

MONOGRAPHS

Alprenolol hydrochloride (0876)**Amiloride hydrochloride (0651)**

Related substances: in line with the general monograph *Substances for pharmaceutical use (2034)* an explicit acceptance criterion for unspecified impurities has been introduced.

Amlodipine besilate (1491)

Related substances: methanol has been replaced by acetonitrile for the dissolution of impurity A in reference solution (d); relative retention of impurity A has been deleted.

Azaperone for veterinary use (1708)

Related substances: in line with the general monograph *Substances for pharmaceutical use (2034)* an explicit acceptance criterion for unspecified impurities has been introduced.

Belladonna leaf (0221)

Identification B: illustration of powdered herbal drug introduced.

Butcher's broom (1847)

Identification C: conditions for HPTLC added.

Assay: the final liquid-liquid purification step has been deleted since degradation was reported during the evaporation of butanol; the simplified procedure proved to be more precise, more accurate and less time consuming.

Carbamazepine (0543)

Related substances: run time extended to allow detection of impurity F; limit for specified impurities A and E increased to 0.15 per cent; impurity G introduced to transparency list under 'Other detectable impurities'.

Carbasalate calcium (1185)

Related substances: the photometric tests for related substances and for impurity C have been replaced by a common LC procedure; the test for impurity C has therefore been deleted and the limits have been updated in view of current batch data obtained using the new method; the transparency list has been extended.

Desoxycortone acetate (0322)

Related substances: in line with the general monograph *Substances for pharmaceutical use (2034)* an explicit acceptance criterion for unspecified impurities has been introduced.

Dexamethasone (0388)

Specific optical rotation: dioxan replaced by anhydrous ethanol to avoid its use, and limits revised accordingly.

Related substances: the limits have been revised based on current batch data; the current LC procedure has been kept with minor modifications; in line with the general monograph *Substances for pharmaceutical use (2034)* an explicit acceptance criterion for unspecified impurities has been introduced.

Impurities: section newly introduced based on available data.

Dexamethasone acetate (0548)

Characters: solubility in acetone deleted.

Identification: chloroform replaced by methylene chloride for IR test.

Specific optical rotation: dioxan replaced by anhydrous ethanol to avoid its use.

Related substances: test revised in order to introduce a list of impurities and update limits according to current product quality.

Dihydrostreptomycin sulphate for veterinary use (0485)

Identification: small change made in the preparation of the reference solution in order to reduce the amount of CRS used.

Assay: clarification of the description of determining the content of streptomycin sulphate and dihydrostreptomycin sulphate.

Ethinylestradiol (0140)

Characters: polymorphism statement introduced for information.

Specific optical rotation: test deleted since no alternative to pyridine could be found.

Related substances: new LC procedure introduced; limits section revised in view of quality of current products; additional impurities described in transparency list.

Gemfibrozil (1694)

Related substances: buffer modified in order to prevent potential precipitation.

Misoprostol (1731)

Related substances: new LC procedure introduced, used also for Assay; limits and transparency list updated based on current batch data.

Diastereoisomers: test revised and new limit prescribed in view of quality of current products.

Mullein flower (1853)

Identification B: illustration of powdered herbal drug introduced.

Nitrazepam (0415)

Identification: set of tests simplified, only IR kept.

Related substances: TLC replaced by LC; transparency list extended.

Heavy metals: test deleted in view of low prescribed dose.

Stramonium leaf (0246)

Identification B: illustration of powdered herbal drug introduced.

Tetracosactide (0644)

Related peptides: further to the establishment of *tetracosactide* CRS batch 3, the leaflet provided with the reference standard has been updated; the solvent volume to be used to dissolve the contents of a vial of the CRS is now prescribed and the resulting concentration takes account of the expansion volume caused by the presence of an excipient in the CRS; the concentrations of the test solution and reference solution (a) have been adapted accordingly.

Ursodeoxycholic acid (1275)

Identification A: sample preparation deleted as superfluous.

Impurity C: TLC kept for this test; reference solutions (b) and (c) revised to use less *lithocholic acid* CRS.

Related substances: TLC replaced by LC in accordance with current policy; impurities H and I added to transparency list under 'Other detectable impurities'.