Comments concerning revised texts published in Supplement 9.4

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the March 2017 session and published in Supplement 9.4.

When a text has been technically revised, this is indicated by horizontal or vertical lines in the margin of the supplement. The details given below complete this information, but are not necessarily exhaustive.

The following details can also be consulted in the Knowledge database under View history.

GENERAL CHAPTERS

2.2.8. Viscosity

Alternative equipment: wording clarified.

2.2.32. Loss on drying

Equipment qualification: the new *sodium aminosalicylate dihydrate CRS* replaces amoxicillin trihydrate.

2.4.2. Arsenic

Method A: modified to avoid use of mercuric bromide paper; new method still relies on same chemical principle.

2.4.31. Nickel in hydrogenated vegetable oils

The temperature programme of the graphite furnace may be different for each device, the text has been modified accordingly.

2.5.12. Water: semi-micro determination

Equipment qualification: the new *sodium aminosalicylate dihydrate CRS* replaces amoxicillin trihydrate.

2.5.32. Water: micro determination

Equipment qualification: the new *sodium aminosalicylate dihydrate CRS* replaces amoxicillin trihydrate.

3.1.3. Polyolefins

Phenolic antioxidants: due to the instability of *plastic additive 12 CRS* in the solvent mixture, it has been indicated to prepare the concerned solutions immediately before use.

3.1.5. Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations

Phenolic antioxidants: due to the instability of *plastic additive 12 CRS* in the solvent mixture, it has been indicated to prepare the concerned solutions immediately before use.

3.1.6. Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations

Phenolic antioxidants: due to the instability of *plastic additive 12 CRS* in the solvent mixture, it has been indicated to prepare the concerned solutions immediately before use.

5.8. Pharmacopoeial harmonisation

Information modified for 2 excipients and added for 2 excipients.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include new monographs published in Supplement 9.4.

DOSAGE FORMS

Capsules (0016)

Gastro-resistant capsules: possible ways to produce gastro-resistant capsules clarified.

Preparations for inhalation (0671)

The following changes have been made in order to align with the EMA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products.

Labelling: delivered dose indicated on label; indication of pre-metered dose only permitted with justification and approval by the competent authority.

Liquid preparations for nebulisation: addition of uniformity requirements.

Pressurised metered-dose preparations for inhalation: addition of leak rate test.

Inhalation powders: wording changed to pre-metered and device-metered inhalers.

The following additional changes have also been made.

Production: instructions for uniformity of delivered dose testing (intra- and inter-inhaler testing) clarified.

Preparations to be converted into vapour: definition harmonised with dosage forms covered in Standard Terms.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Artichoke leaf (1866)

Assay: *artichoke leaf dry extract HRS* introduced for system suitability test; resolution requirement replaced by peak-to-valley ratio between chlorogenic acid and cryptochlorogenic acid.

Artichoke leaf dry extract (2389)

Assay: description of the column changed; peak eluting immediately after chlorogenic acid identified as cryptochlorogenic acid and described as such in the peak-to-valley ratio requirement.

MONOGRAPHS

Albendazole (1386)

Definition: content limits tightened.

Characters: statement on polymorphism added.

Identification: method of sample preparation no longer specified; recrystallisation procedure added since substance shows polymorphism.

Related substances: LC revised to reflect impurity profiles of products available on European market; limits modified and 1 additional specified and 5 additional unspecified impurities now controlled by revised method.

Impurities: section updated.

Basic butylated methacrylate copolymer (1975)

Definition: relative molecular mass updated following development of a more accurate size-exclusion chromatography method in place of viscometry, which was used during elaboration of the monograph.

Benzyl alcohol (0256)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter *5.8. Pharmacopoeial harmonisation*.

Carmellose calcium (0886)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter *5.8. Pharmacopoeial harmonisation*.

In addition, modifications made to align to document signed by the PDG.

Cefixime (1188)

Related substances: updated to include statement that solutions are to be prepared immediately before use and a refrigerated autosampler at 4 °C is to be used.

Ethanol: updated to use *dimethylformamide R* as the solvent for sample preparation.

Assay: symmetry factor of maximum 3.0 introduced for the peak due to cefixime.

Chlorhexidine diacetate (0657)

Identification: the 2nd identification series has been updated and consists of a new TLC method and the reaction of acetates.

Chlorhexidine dihydrochloride (0659)

Identification: the 2nd identification series has been updated and consists of a new TLC method and the reaction of chlorides.

Clarithromycin (1651)

Related substances: quantity of *clarithromycin for peak identification CRS* used in reference solution (d) reduced; volume of solution reduced accordingly.

Colchicine (0758)

Identification: IR sample preparation deleted in accordance with current policy.

Related substances: specifications updated; impurity B (conformational isomer) excluded from the total; impurity G added as a specified impurity.

Chloroform: test deleted.

Dextran 1 for injection (1506)

Identification B: wording improved and blank omitted.

Sodium chloride: colorimetric end-point determination replaced by potentiometry to avoid the use of potassium chromate (REACH Annex XIV).

Dosulepin hydrochloride (1314)

Identification B: IR sample preparation deleted in accordance with current policy.

Related substances: title of test modified; acceptance criterion for unspecified impurities introduced; 'Identification of impurities' section added; name of CRS used for system suitability changed.

Impurities: section updated.

Ethosuximide (0764)

***Identification*:** IR sample preparation deleted in accordance with current policy; 2nd identification series updated to avoid use of cobalt chloride (test D) and now consists of melting point and new TLC method.

Related substances: GC replaced by core-shell LC method.

Impurities: impurity B added.

Fentanyl (1210)

Characters: solubility in lipophilic solvent added.

Identification: reference spectrum replaced by reference substance.

Related substances: more robust UHPLC method introduced; limits updated.

Assay: end-point determination by colour indicator replaced by potentiometry.

Impurities: transparency list updated.

Fentanyl citrate (1103)

Characters: solubility in lipophilic solvent added.

Identification: reference spectrum replaced by reference substance.

Related substances: more robust UHPLC method introduced; limits updated.

Assay: end-point determination by colour indicator replaced by potentiometry.

Impurities: transparency list updated.

Furosemide (0391)

Identification: 2nd identification series updated to replace UV and chemical identification with TLC.

Gonadorelin acetate (0827)

Characters: hygroscopic character of the powder added.

Identification: TLC test replaced by NMR and the test for amino acid analysis moved to this section in line with other peptide monographs; *gonadorelin for NMR identification CRS* introduced; tests A and B or tests A and C may alternatively be carried out, in accordance with current policy; the methods to be used for hydrolysis and analysis in the amino acid analysis are presented in a more flexible manner as this test is now prescribed only for identification purposes.

Specific optical rotation: limits tightened based on current batch data.

Absorbance: non-specific test deleted as there is no added value compared to the other purity tests.

Related substances: *gonadorelin for system suitability CRS* and a system suitability criterion introduced; limits for specified and unspecified impurities, as well as a reporting threshold, also introduced.

Water: semi-micro determination replaced by coulometric titration which uses a smaller amount of test sample.

Bacterial endotoxins: test deleted as this aspect is now covered by the general monograph *Substances for pharmaceutical use (2034)* in line with the European Pharmacopoeia policy on bacterial endotoxins in substances for pharmaceutical use (February 2015).

Labelling: statement on the suitability of the substance for use in the manufacture of parenteral preparations added, in accordance with current policy.

Impurities: section introduced.

Gonadotrophin chorionic (0498)

Production: the requirements for viral safety have been updated and harmonised across monographs on urine-derived substances. The emphasis is placed on the production, i.e. the clearance of viruses by the manufacturing process, rather than on tests for specific viruses /

viral antigens. A statement has been reintroduced to make it clear that the manufacturing process should be demonstrated to inactivate and/or remove extraneous agents. As stated in the general monograph *Substances for pharmaceutical use (2034)*, the requirements of general chapter *5.1.7. Viral safety* apply to the manufacture of urine-derived substances.

Guaifenesin (0615)

Identification C: spraying solution replaced to improve detection.

Related substances: maximum daily dose higher than 2 g/day, therefore specifications revised.

Assay: method replaced by LC used for related substances.

Imipenem monohydrate (1226)

Related substances: storage of HPLC vials at 5 °C using a temperature controlled autosampler introduced.

Isomalt (1531)

Related substances: sample and solvent amounts reduced.

Water: water-free formamide used.

Levetiracetam (2535)

Characters: solubility in hexane replaced by less toxic solvent heptane.

Enantiomeric purity: hexane replaced by heptane.

Impurity C: test deleted, as this impurity is now controlled by the LC for related substances.

Impurity G: LC test introduced.

Related substances: new LC method introduced for the control of additional impurities; limits updated.

Impurities: section updated.

Methylprednisolone acetate (0933)

Related substances: limit for impurity A increased.

Methylrosanilinium chloride (1990)

Definition: reference to pentamethyl-*p*-rosanilinium deleted.

Related substances: former test for pentamethyl-*p*-rosanilinium and former related substances test merged in new related substances test; acceptance criterion for unspecified impurities introduced; ‘Identification of impurities’ and ‘Relative retention’ sections added; expression of limits updated.

Impurities: section updated to include pentamethyl-*p*-rosanilinium (impurity B).

Metoclopramide (1348)

Identification B: recrystallisation procedure added as substance shows polymorphism.

Identification C: reference solution now prepared without *sulpiride CRS*.

Impurity E: retardation factors added.

Related substances: method modified to improve separation of impurities in reproducible order of elution; impurity limits updated; acceptance criterion for unspecified impurities introduced; reporting threshold updated in line with current policy.

***Impurities*:** section updated.

Metoclopramide hydrochloride monohydrate (0674)

Title, Definition: degree of hydration added.

Identification B: IR sample preparation deleted in accordance with current policy.

Identification C: previous TLC slightly changed.

Impurity E: former TLC for related substances used with some modifications.

Related substances: TLC replaced by LC to control impurities A, B, C, D, F, G and H.

Impurities: section added.

Paracetamol (0049)

Identification: 1st identification series updated and only IR now required; IR sample preparation deleted in accordance with current policy; 2nd identification series updated to avoid using potassium dichromate (test D) and only a mixed melting point now described.

Related substances: new LC to take into account additional impurities.

Sodium cetostearyl sulfate (0847)

Water: sample size reduced.

Sucralfate (1796)

Content : upper limit for sucrose octasulfate increased to 38.0 per cent; lower limit for aluminium decreased to 15.5 per cent.

Temozolomide (2780)

Related substances: limits for impurities D and E increased.

Urofollitropin (0958)

Production: the requirements for viral safety have been updated and harmonised across monographs on urine-derived substances. The emphasis is placed on the production, i.e. the clearance of viruses by the manufacturing process, rather than on tests for specific viruses / viral antigens. Such tests are no longer listed in the monograph and have been replaced by a statement which has been reintroduced in the Production section to make it clear that the manufacturing process should be demonstrated to inactivate and/or remove extraneous agents. As stated in the general monograph *Substances for pharmaceutical use (2034)*, the requirements of general chapter *5.1.7. Viral safety* apply to the manufacture of urine-derived substances.

Tests: the tests for hepatitis virus antigens and HIV antigen have been deleted. The decision to test for certain viruses is made on a case-by-case basis, based on a risk assessment and depending on the viral safety measures already in place. Thus, the fact that tests for specific viruses are no longer included in the monograph should not be understood as a sign that such testing is not relevant.

Urokinase (0695)

Production: the requirements for viral safety have been updated and harmonised across monographs on urine-derived substances. The emphasis is placed on the production, i.e. the clearance of viruses by the manufacturing process, rather than on tests for specific viruses / viral antigens. Such tests are no longer listed in the monograph and have been replaced by a statement which has been reintroduced in the Production section to make it clear that the manufacturing process should be demonstrated to inactivate and/or remove extraneous agents. As stated in the general monograph *Substances for pharmaceutical use (2034)*, the requirements of general chapter *5.1.7. Viral safety* apply to the manufacture of urine-derived substances.

Tests: the test for hepatitis B surface antigen has been deleted. The decision to test for certain viruses is made on a case-by-case basis, based on a risk assessment and depending on the viral safety measures already in place. Thus, the fact that tests for specific viruses are no longer included in the monograph should not be understood as a sign that such testing is not relevant.

Vinorelbine tartrate (2107)

Related substances: method modified to improve separation of impurities; new Impurity K added and specifications updated based on data from manufacturers.

Bacterial endotoxins: test deleted.

Impurities: section updated.

Water, purified (0008)

In line with the Ph. Eur. implementation strategy for the ICH Q3D guideline for elemental impurities, the test for heavy metals *(2.4.8)* has been deleted.

However, to retain the aspect of control for elemental impurities, the ‘Purified water in bulk’ section of the monograph has been revised to address the situation where purified water in bulk does not comply with the requirements for conductivity prescribed in *Water for injections (0169)* in bulk.