Comments concerning revised texts published in Supplement 9.1

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the March 2016 session and published in Supplement 9.1.

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

2.2.14. Melting point - capillary method

This general chapter has been merged with general chapter *2.2.60. Melting point - instrumental method*, and both approaches (i.e. manual and automated) are now described. A system suitability test has been introduced. Calibration of the instrument is performed with certified reference materials according to the instrument manufacturer's requirements.

2.7.5. Assay of heparin

Anti-factor IIa activity, Anti-factor Xa activity: the text has been revised to introduce more flexibility in the concentration ranges to be used for the tests.

2.9.14. Specific surface area by air permeability

Apparatus (b)-U-tube manometer: *dibutyl phthalate R*, a reagent on the REACH list, replaced by the liquid recommended by the manufacturer of the equipment or water.

2.9.40. Uniformity of dosage units

The text is revised as follows to implement the PDG sign-off document in November 2015.

Introduction: the chapter does not apply to single-dose solutions, suspensions, emulsions or gels for local action following cutaneous application.

Table 2.9.40.-1: examples added to category 'Others'.

5.8. Pharmacopoeial harmonisation

2.9.40. Uniformity of Dosage units: changes reflect implementation of the PDG sign-off document in November 2015.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include the new monographs published in the 9th Edition and in Supplement 9.1.

GENERAL MONOGRAPHS

Substances for pharmaceutical use (2034)

Related substances. The reference to the EMA guideline on the limits of genotoxic impurities has been replaced by a reference to the new ICH guideline M7 *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.

Bacterial endotoxins. The requirements associated with the test have been clarified and aligned with the European Pharmacopoeia policy on bacterial endotoxins in substances for pharmaceutical use (see Pharmeuropa - Technical information - version September 2014, revised February 2015). This revision goes hand-in-hand with the revision of general chapter *5.1.10. Guidelines for using the test for bacterial endotoxins*, published in Supplement 8.8, which includes recommendations for establishing limits and information on how to evaluate the pyrogenicity of substances.

VACCINES FOR HUMAN USE

Poliomyelitis vaccine (oral) (0215)

This monograph has been revised to harmonise requirements with WHO regulations and also to reflect the profile for the control of production intermediates that European producers actually apply for oral poliomyelitis vaccines. Indeed, since the end of 2012, WHO recommendations extended the use of the neurovirulence test in transgenic mice to seed lots as a replacement for the test in monkeys and also allowed the MAPREC assay to be used as a genetic marker test for types 1 and 2 in addition to type 3.

The revision includes: extension of the MAPREC assay as a genetic marker test to monitor the consistency of production of all poliomyelitis types on seed lots, single harvests and monovalent bulks; introduction of the International Standard for poliovirus type 1 for MAPREC; modification of the wording for the neurovirulence test to introduce the recommended use of transgenic mice instead of monkeys (the test cross-references the detailed WHO procedure); the introduction of alternative molecular methods to MAPREC.

The monograph has been also revised in light of the 3rd WHO Global Action Plan (GAPIII) on poliomyelitis eradication. Part of the eradication strategy is withdrawal of poliomyelitis virus type 2 from the vaccine and its use under high level control and containment conditions. As a result of the upcoming requirements, the Poliomyelitis vaccine (oral) BRP (OPV BRP) from the EDQM has been discontinued and the reference to the OPV BRP has been deleted.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Angelica sinensis root (2558)

Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Salvia miltiorrhiza root and rhizome (2663)

Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Assay: criterion for symmetry factor for peak due to salvianolic acid B is less stringent.

Valerian root (0453)

Assay of essential oil: xylene replaced by 1,2,4-trimethylbenzene.

Valerian root, cut (2526)

Assay of essential oil: xylene replaced by 1,2,4-trimethylbenzene.

HOMEOPATHIC PREPARATIONS

Homoeopathic preparations (1038)

Manufacturing methods: Table 1038.-1 updated following revision of monograph *Methods of preparation of homoeopathic stocks and potentisation (2371)*.

Homoeopathic pillules, impregnated (2079)

Production: introduction of approach used in French tradition regarding impregnation step.

MONOGRAPHS

Alfuzosin hydrochloride (1287)

Related substances: a temperature of 25 °C is indicated to allow optimal separation of impurities; in addition, the system suitability criterion has been amended.

Impurities: transparency list updated.

Atenolol (0703)

Related substances: correction factor for impurity I deleted and impurity J now identified and specified.

Bacitracin (0465)

Composition: method improved and new limits given.

Related substances: test added; individual limits given for 13 specified impurities; limit for total impurities and for 'any other impurity' introduced.

Related peptides, Impurity E: tests incorporated into tests for composition and related substances.

Bacterial endotoxins: test removed as limits to be based on the daily dose & finished product.

Sterility: test removed as the requirement for sterility is the responsibility of the user.

Impurities: structures provided for newly introduced impurities to the extent known.

Bacitracin zinc (0466)

Composition: method improved and new limits given.

Related substances: test added; individual limits given for 13 specified impurities; limit for total impurities and for 'any other impurity' introduced.

Related peptides, Impurity E: tests incorporated into tests for composition and related substances.

Zinc: the limits have been adjusted based on available batch data.

Sterility: test removed as the requirement for sterility is the responsibility of the user.

Pyrogens: test removed as this substance is not known to be used for parenteral products.

Impurities: structures provided for newly introduced impurities to the extent known.

Bromhexine hydrochloride (0706)

Content: limits updated to reflect change of assay method.

Identification: 2nd identification series updated.

Assay: titration replaced by LC from related substances test.

Caprylocaproyl macrogolglycerides (1184)

Functionality-related characteristics: this section has been added. Caprylocaproyl macrogolglycerides are used as self-emulsifying agents and solubilisers. The tests for Hydroxyl value, Saponification value and Composition of fatty acids are cross-referenced.

Chloramphenicol (0071)

Content: lower limit updated to reflect change in assay method.

Identification: for the 1st identification series, IR is sufficient and for the 2nd identification series, mixed melting point is sufficient.

Related substances: TLC replaced by LC; limits introduced for specified, unspecified and total impurities.

Pyrogens: test removed as substance not known to be used for parenteral products.

Assay: UV absorbance replaced by LC for related substances.

Impurities: section added describing impurities controlled by LC.

Dicycloverine hydrochloride (1197)

Related substances: TLC replaced by LC and specifications updated.

Loss on drying: replaced by micro determination of water.

Estradiol hemihydrate (0821)

Related substances: *estradiol for peak identification CRS* now used for system suitability; description of *estradiol for peak identification CRS* amended.

Etoposide (0823)

Water: method 2.5.12 replaced by method 2.5.32 (evaporation technique).

Lauroyl macrogolglycerides (1231)

Functionality-related characteristics: this section has been added. Lauroyl macrogolglycerides are used as self-emulsifying agents, solubilisers, modified-release agents and wetting agents for powders and tablets. The tests for Hydroxyl value, Saponification value and Composition of fatty acids are cross-referenced.

Linoleoyl macrogolglycerides (1232)

Functionality-related characteristics: this section has been added. Linoleoyl macrogolglycerides are used as self-emulsifying agents and solubilisers. The tests for Hydroxyl value, Saponification value and Composition of fatty acids are cross-referenced.

Montelukast sodium (2583)

Enantiomeric purity: following establishment of montelukast racemate CRS batch 3, the wording of reference solution (b) has been modified.

Oleoyl macrogolglycerides (1249)

Functionality-related characteristics: this section has been added. Oleoyl macrogolglycerides are used as self-emulsifying agents and solubilisers. The tests for Hydroxyl value, Saponification value and Composition of fatty acids are cross-referenced.

Phenoxymethylpenicillin (0148)

Definition: production restricted to the use of *Penicillium notatum* or related microorganisms.

Specific optical rotation: test removed as purity is controlled by LC for related substances.

Related substances: introduction of improved method; limits reflect the quality of current batches on the market.

Assay: same method as described for related substances test.

Phenoxymethylpenicillin potassium (0149)

Definition: production restricted to the use of *Penicillium notatum* or related microorganisms.

Specific optical rotation: test removed as purity is controlled by LC for related substances.

Related substances: introduction of improved method; limits reflect the quality of current batches on the market.

Assay: same method as described for related substances test.

Pholcodine monohydrate (0522)

Title: the degree of hydration has been specified.

Related substances: additional specified impurity added.

Sesame oil, refined (0433)

Composition of triglycerides: the limit range for triolein (OOO) content has been modified.

Sitagliptin phosphate monohydrate (2778)

IR identification: methanol now used as solvent instead of anhydrous ethanol.

Sodium starch glycolate (type A) (0983)

Functionality-related characteristics: section added. Sodium starch glycolate (type A) is used as disintegrant in tablets. By analogy with croscarmellose sodium, settling volume, degree of substitution and particle-size distribution are stated. The method for degree of substitution provided in the monograph *Croscarmellose sodium (0985)* is also added for Sodium starch glycolate.

Sodium starch glycolate (type B) (0984)

Functionality-related characteristics: section added. Sodium starch glycolate (type B) is used as disintegrant in tablets. By analogy with croscarmellose sodium, settling volume, degree of substitution and particle-size distribution are stated. The method for degree of substitution provided in the monograph *Croscarmellose sodium (0985)* is also added for Sodium starch glycolate.

Sorbitan laurate (1040)

Functionality-related characteristics: this section has been added. Sorbitan laurate is used as an emulsifier and co-solubiliser in creams. Sorbitan esters are mixtures of sorbitan esterified with fatty acids. The test for Composition of fatty acids is cross-referenced, as it gives an indication of the lipophilicity of the substance. In addition, the test for Hydroxyl value is cross-referenced, as it gives an indication of the hydrophilicity of sorbitan.

Sorbitan oleate (1041)

Functionality-related characteristics: this section has been added. Sorbitan oleate is used as an emulsifier and co-solubiliser in creams. Sorbitan esters are mixtures of sorbitan esterified with fatty acids. The test for Composition of fatty acids is cross-referenced, as it gives an indication of the lipophilicity of the substance. In addition, the test for Hydroxyl value is cross-referenced, as it gives an indication of the hydrophilicity of sorbitan.

Sorbitan palmitate (1042)

Functionality-related characteristics: this section has been added. Sorbitan palmitate is used as an emulsifier and co-solubiliser in creams. Sorbitan esters are mixtures of sorbitan esterified with fatty acids. The test for Composition of fatty acids is cross-referenced, as it gives an indication of the lipophilicity of the substance. In addition, the test for Hydroxyl value is cross-referenced, as it gives an indication of the hydrophilicity of sorbitan.

Sorbitan sesquioleate (1916)

Functionality-related characteristics: this section has been added. Sorbitan sesquioleate is used as an emulsifier and co-solubiliser in creams. Sorbitan esters are mixtures of sorbitan esterified with fatty acids. The test for Composition of fatty acids is cross-referenced, as it gives an indication of the lipophilicity of the substance. In addition, the test for Hydroxyl value is cross-referenced, as it gives an indication of the hydrophilicity of sorbitan.

Sorbitan stearate (1043)

Functionality-related characteristics: this section has been added. Sorbitan stearate is used as an emulsifier and co-solubiliser in creams. Sorbitan esters are mixtures of sorbitan esterified with fatty acids. The test for Composition of fatty acids is cross-referenced, as it gives an indication of the lipophilicity of the substance. In addition, the test for Hydroxyl value is cross-referenced, as it gives an indication of the hydrophilicity of sorbitan.

Sorbitan trioleate (1044)

Functionality-related characteristics: this section has been added. Sorbitan trioleate is used as an emulsifier and co-solubiliser in creams. Sorbitan esters are mixtures of sorbitan esterified with fatty acids. The test for Composition of fatty acids is cross-referenced, as it gives an indication of the lipophilicity of the substance. In addition, the test for Hydroxyl value is cross-referenced, as it gives an indication of the hydrophilicity of sorbitan.

Stearoyl macrogolglycerides (1268)

Functionality-related characteristics: this section has been added. Stearoyl macrogolglycerides are used as self-emulsifying agents, solubilisers, modified-release agents and wetting agents. The tests for Hydroxyl value, Saponification value and Composition of fatty acids are cross-referenced.

Vecuronium bromide (1769)

Related substances: mobile phase composition adjusted; system suitability criteria modified; impurity limits updated based on current batch data.

Impurities: section updated.

Water for injections (0169)

Production: revision to include purification processes equivalent to distillation (such as reverse osmosis coupled with appropriate techniques) for producing water for injections (WFI), in addition to distillation; use of non-distillation technologies for the production of WFI requires that notice is given to the supervisory authority of the manufacturer before implementation.

A requirement for regular monitoring of total organic carbon has been added to further emphasise the specific test controls required in the Production section.

The revision of the monograph is supported by the evidence provided in the document ‘Reverse osmosis in Ph. Eur. monograph *Water for injections (0169)*’, published in the Knowledge database under ‘Additional information’.