Comments concerning revised texts published in Supplement 8.6

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November 2014 session and published in Supplement 8.6.

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

2.2.4. Approximate pH of solutions

Use of widely used, commercially available pH indicator strips now permitted.

2.2.19. Amperometric titration

Reference to mercury-containing electrodes deleted.

2.2.20. Potentiometric titration

General method updated to introduce modern autotitrator instruments; reference to mercury-containing electrodes deleted following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

2.2.34. Thermal analysis

This general chapter has been revised to indicate its status within the context of International 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.

Thermogravimetry: more details given on temperature calibration and on test conditions; to harmonise with the JP, final temperature of 250 °C and heating rate of 5 °C/min given as examples for calibration of the electrobalance.

Differential scanning calorimetry: more details given on temperature calibration and heat-quantity calibration.

Thermomicroscopy: section deleted as typically considered part of optical microscopy and not thermal analysis.
2.2.36. Potentiometric determination of ionic concentration using ion-selective electrodes

Deletion of the reference to calomel electrodes, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

2.4.29. Composition of fatty acids in oils rich in omega-3 acids

The chapter has been clarified by rephrasing some text passages; in addition the procedure has been made more user-friendly: temperature program for splitless injection introduced; adjustment of split ratio and/or sample dilution in order to obtain suitable symmetry factors introduced; system suitability simplified: i) theoretical response factors and adjustment for the actual weight introduced, so it is no longer required that an exact equal amount of each component of reference solution (b) be weighed; ii) resolution now based on fatty acid esters already present in the test solution, therefore reference solution (c) is prepared only for triglycerides if necessary.

2.5.5. Peroxide value

2 editorial modifications have been made: sample sizes in Table 2.5.5.-1 have been inverted to be consistent with the expected peroxide values; the term ‘impure’ has been deleted.

2.5.32. Water: micro determination

The main changes concern: the recommendation to determine quantities of water greater than 100 µg; the possibility of using a suitable certified reference material for instrument qualification; increased flexibility for the frequency of the verification of accuracy.

2.9.3. Dissolution test for solid dosage forms

This chapter has been revised to indicate its status within the context of International 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.

2.9.40. Uniformity of dosage units

This chapter has been revised to indicate its status within the context of International 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.

Preparations supplied in single-dose containers that represent 1 dose of medicinal product and are intended for transdermal delivery of the active substance(s) in view of a systemic effect, including solutions, comply with the general chapter.

Multivitamin, single-vitamin and trace-element preparations are excluded from the scope of the test for content uniformity.

5.2.4. Cell cultures for the production of veterinary vaccines

*Retrovirus*: addition of retrovirus testing on cell lines and primary cells.
5.8. Pharmacopoeial harmonisation

Additional information is presented for 4 monographs on excipients and 3 general chapters and information is modified for 2 monographs on excipients.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs published in Supplement 8.6.

VACCINES FOR VETERINARY USE

Brucellosis vaccine (live) (Brucella melitensis Rev. 1 strain) for veterinary use (0793)

The reference strain ‘Brucella melitensis Rev. 1 strain BRP’ has been replaced by a suitable reference strain of Brucella melitensis Rev. 1. A suitable reference strain is available from the OIE Reference Laboratory for Brucellosis at ANSES, Unité zoonoses bactériennes, 94706 Maisons-Alfort, France.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Pentetate sodium calcium for radiopharmaceutical preparations (2353)

Definition: updated to include a ‘variable quantity of water’ according to current Ph. Eur. policy on hydrates.

Technetium (99mTc) medronate injection (0641)

Identification C: improved TLC to distinguish medronate and oxidronate.

Tin: limit now expressed in mg per maximum recommended dose in mL; use of a test kit which allows determination of low amounts of tin.

Physiological distribution: test deleted as all remaining tests considered sufficient to confirm the identity and quality of the preparation.

Bacterial endotoxins: test with specific limit introduced.

Radiochemical purity: reference solutions introduced for comparison purposes in identification test B.
HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Benzoin, Siam (2158)

Definition: minimum requirement for total acids lowered.

Identification: macroscopic description improved; TLC conditions updated and HPTLC conditions introduced.

Bilberry fruit, dried (1588)

Identification C: pure reference compound replaced by bilberry dry extract HRS; HPTLC conditions added.

Bilberry fruit, fresh (1602)

Identification C: pure reference compound replaced by bilberry dry extract HRS; HPTLC conditions added.

Centella (1498)

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

Tests: test for adulteration with Bacopa monnieri L. introduced; maximum limit for loss on drying increased and maximum limit of 2 per cent for ash insoluble in hydrochloric acid introduced.

Assay: gradient table modified; system suitability test introduced; centella dry extract HRS introduced for peak identification and asiaticoside CRS introduced for quantification.

Fresh bilberry fruit dry extract, refined and standardised (2394)

Identification A: pure reference compounds replaced by bilberry dry extract HRS; TLC/HPTLC improved and harmonised with the monographs on Fresh bilberry fruit (1602) and Dried bilberry fruit (1588).

Ginseng (1523)

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

Java tea (1229)

Identification B: microscopic identification updated.

Identification C: HPTLC conditions and 2nd reference compound introduced; results table updated.

Assay: the assay of the marker sinensetin has been replaced by an assay of rosmarinic acid, since rosmarinic acid is commonly used in the assay of herbal drug preparations of Java tea and is more suitable for stability studies.
HOMOEOPATHIC PREPARATIONS

Methods of preparation of homoeopathic stocks and potentisation (2371)

*Method 5.2 LM potencies*: new method added.

MONOGRAPHS

**Aluminium phosphate, hydrated (1598)**

*Definition*: it is now stated that the substance contains a variable quantity of water.

**Amidotrizoic acid dihydrate (0873)**

*Assay*: deletion of the reference to the mercurous sulfate electrode, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

**Amiloride hydrochloride dihydrate (0651)**

*Title*: title modified according to current Ph. Eur. policy on hydrates.

*Characters*: solubility in a lipophilic solvent introduced.

*Identification*: reference to test for Water added as Identification E.

*Related substances*: new LC introduced to control additional impurities.

**Amlodipine besilate (1491)**

*Related substances*: amounts of reference standards reduced.

**Anticoagulant and preservative solutions for human blood (0209)**

*Identification A*: name of CRS modified to indicate degree of hydration; system suitability performed using reagents instead of CRSs (valid for ACD and CPD).

**Aprotinin (0580)**

*Assay*: deletion of the reference to calomel electrodes, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

**Aprotinin concentrated solution (0579)**

*Assay*: deletion of the reference to calomel electrodes, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

**Bromhexine hydrochloride (0706)**

*Related substances*: improved LC method introduced; limits for impurities reviewed, based on current batch data. Explicit acceptance criterion for unspecified impurities added.
Buserelin (1077)

**Related substances, Assay:** LC revised to improve resolution and allow detection of 2 additional impurities; impurity limits tightened based on current batch data; distinction made between specified and unspecified impurities according to the thresholds for synthetic peptide impurities, as stated in the general monograph *Substances for pharmaceutical use (2034).*

**Impurities:** section updated and 2 new specified impurities added.

Carbomers (1299)

**Apparent viscosity (FRC):** deletion of reference to calomel electrodes, following entry into force of EU Regulation 847/2012 restricting use of mercury in measuring devices.

Carnauba wax (0597)

**Appearance of solution:** test deleted as substance not used parenterally and the method includes a reagent proscribed under the REACH regulation (potassium dichromate).

Chymotrypsin (0476)

**Assay:** deletion of the reference to calomel electrodes, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Crosopovidone (0892)

This monograph has been revised to indicate its status within the context of International 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.*

Demeclocycline hydrochloride (0176)

**Related substances:** the elution order of impurities A and B has been exchanged.

Dihydralazine sulfate, hydrated (1310)

**Assay:** deletion of the reference to calomel electrodes, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Diphenhydramine hydrochloride (0023)

**Identification C:** sample preparation deleted.

**Identification D:** only test (a) for chlorides is now prescribed as potassium dichromate used in test (b) is proscribed under the REACH regulation.

Dithranol (1007)

**Assay:** deletion of the reference to calomel electrodes, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Doxapram hydrochloride (1201)

**Definition:** degree of hydration added.
Filgrastim concentrated solution (2206)

**Definition:** minimum potency limit lowered, to correspond to the actual minimum potency, in line with the general policy for other biological monographs; the new value is based on recent batch data.

**Identification:** cross-reference to test for related proteins added.

**Impurities with molecular masses higher than that of filgrastim:** in line with current practice, a limit for the sum of aggregates and oligomers has been introduced, as well as a limit for total impurities with molecular masses higher than that of filgrastim.

**Related proteins:** introduction of a new LC method which is simpler and allows better resolution of the reduced forms that elute after the principal peak; resolution between the peak due to oxidised filgrastim (form 2) and the principal peak also improved. 2 quantitative criteria for system suitability for new method introduced.

**Assay (potency):** it is specified that the recommended cell line made sensitive to G-CSF is suitable for use.

Fluticasone propionate (1750)

**Content:** lower limit tightened to take revision of total impurities into account.

**Identification:** reference to LC deleted, as identification by IR is sufficient.

**Related substances:** isocratic step introduced to gradient; limits updated based on current batch data.

**Assay:** retention time of fluticasone propionate, relative retention of impurity D and run time introduced. Preparation of test solution and reference solutions modified to take into account possible solubility issues.

**Impurities:** certain specified impurities reclassified as other detectable impurities.

Fructose (0188)

**Characters:** reference to taste deleted.

**Identification A:** system suitability performed using reagents instead of CRSs.

Fulvestrant (2443)

**Related substances:** quantitative expression of acceptance criteria applied.

**Stereochemical purity:** method modified to improve robustness.

Galactose (1215)

**Identification A:** sample preparation deleted.

**Identification B:** system suitability performed using reagents instead of CRSs.

Glimepiride (2223)

**Impurity A:** batch 2 of glimepiride CRS no longer contains impurity A in significant amounts, therefore glimepiride for impurity A identification CRS is now used.
Glucose, anhydrous (0177)

This monograph has been revised to indicate its status within the context of International 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.

**Definition:** source and limits for content introduced.

**Characters:** solubility in ethanol (96 per cent) corrected; taste deleted.

**Identification:** cross-references to assay (LC) and test for water introduced (1st series); 2nd series introduced for pharmacies; TLC plate using inorganic binder replaced by plate containing organic binder (identification test C) and CRSs replaced by reagents (system suitability test).

**Conductivity:** test for conductivity introduced to replace test for acidity or alkalinity and tests for ions.

**Related substances, Assay:** LC method introduced.

**Dextrin, Soluble starch, sulfite:** tests similar to those included in USP and JP introduced to replace test for foreign sugars, soluble starch, dextrins and test for sulfites.

**Lead:** test deleted as no information presently exists regarding real risk of contamination with lead.

Glucose monohydrate (0178)

This monograph has been revised to indicate its status within the context of International 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.

**Definition:** source and limits for content introduced.

**Characters:** solubility in ethanol (96 per cent) corrected; taste deleted.

**Identification:** cross-references to assay (LC) and test for water introduced (1st series); 2nd series introduced for pharmacies; TLC plate using inorganic binder replaced by plate containing organic binder (identification test C) and CRSs replaced by reagents (system suitability test).

**Conductivity:** test for conductivity introduced to replace test for acidity or alkalinity and tests for ions.

**Related substances, Assay:** LC method introduced.

**Dextrin, Soluble starch, sulfite:** tests similar to those included in USP and JP introduced to replace test for foreign sugars, soluble starch, dextrins and test for sulfites.

**Lead:** test deleted as no information presently exists regarding real risk of contamination with lead.

Hexylresorcinol (1437)

**Related substances:** LC revised to take into account new impurity profiles from products available on the European market; limits updated.

**Impurities:** section updated.
Human coagulation factor IX (rDNA) concentrated solution (2522)

Impurities with molecular masses greater than that of human coagulation factor IX (rDNA): improvements made to the preparation of the resolution solution to ensure that the amount of high molecular mass species (HMM) is sufficient to allow effective testing of system suitability; system suitability criterion for peak-to-valley ratio adjusted; composition of the mobile phase corrected.

Additional changes relate to the preparation of all reference solutions prepared with human coagulation factor IX (rDNA) CRS, which is presented as freeze-dried preparation and not solution.

Hypromellose (0348)

Heavy metals: test now categorised as non-harmonised.

Iopanoic acid (0700)

Assay: deletion of the reference to the mercurous sulfate electrode, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Ioxaglic acid (2009)

Assay: deletion of the reference to mercurous sulfate electrode, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Isoleucine (0770)

Ammonium: presented as a separate limit test from the test for ninhydrin-positive substances.

Lactose, anhydrous (1061)

Definition: description of water solubility modified.

Identification B: system suitability performed using reagents instead of CRSs; TLC silica gel G plate replaced by the more readily available TLC silica gel plate.

Lactose monohydrate (0187)

Definition: description of water solubility modified.

Identification A: name of CRS modified to indicate degree of hydration.

Identification B: name of CRS modified to indicate degree of hydration; system suitability performed using reagents instead of CRSs; TLC silica gel G plate replaced by the more readily available TLC silica gel plate.

Storage: deleted as substance is not hygroscopic.

Leucine (0771)

Ammonium: presented as a separate limit test from the test for ninhydrin-positive substances.
Lysine hydrochloride (0930)

*Ammonium:* presented as a separate limit test from the test for ninhydrin-positive substances.

Methionine (1027)

*Identification:* TLC test for ninhydrin-positive substances now only used for identification C.

*Related substances:* LC introduced.

*Chlorides:* method revised.

Methylcellulose (0345)

*Heavy metals:* test now categorised as non-harmonised.

Methylprednisolone acetate (0933)

*Content:* upper limit updated to reflect change in assay method.

*Characters:* added that substance shows polymorphism.

*Identification:* TLC from 1st identification series replaced by cross-reference to LC for related substances; 2nd identification series deleted as substance not used in pharmacies.

*Specific optical rotation:* dioxan replaced by less-toxic solvent; limits modified accordingly.

*Related substances:* gradient LC method introduced to allow control of additional impurities; limits updated to reflect quality of substances in approved medicinal products on European market.

*Assay:* UV absorbance replaced by modified LC for related substances.

Methylprednisolone hydrogen succinate (1131)

*Content:* limits updated to reflect change in assay method.

*Identification:* TLC from 1st identification series replaced by cross-reference to LC for related substances; 2nd identification series deleted as substance not used in pharmacies.

*Specific optical rotation:* dioxan replaced by less-toxic solvent; limits modified accordingly.

*Related substances:* slightly modified LC method to allow control of additional impurities; limits updated to reflect quality of substances in approved medicinal products on European market.

*Assay:* UV absorbance replaced by LC for related substances.

Methylthioninium chloride (1132)

*Content:* limits updated to reflect change in assay method.

*Definition:* in accordance with current Ph. Eur. policy regarding degree of hydration, it is stated that the substance contains a variable quantity of water.

*Appearance:* hygroscopicity added and terms revised for consistency with Style guide.

*Solubility:* solubility in water corrected.
**Identification**: absorption maxima corrected in Identification A; Identification C deleted as it was not specific enough.

**Methanol-insoluble substances**: test deleted since it was not pertinent.

**Related substances**: LC revised in order to take additional impurities into account.

**Loss on drying**: upper limit increased in order to include the pentahydrate form.

**Assay**: titration replaced by LC used in the test for related substances.

**Storage**: indication of temperature added.

**Impurities**: section updated.

**Naftidrofuryl hydrogen oxalate (1594)**

**Identification A, Related substances (test B)**: reference to rotary evaporator deleted since other equipment or procedures may be used.

**Nicotinamide (0047)**

**Characters**: solubility in lipophilic solvent added.

**Identification**: melting point deleted from 1st identification series as IR is sufficient; TLC added to 2nd identification series in place of former identification tests C (to avoid ammonia inhalation) and D (to avoid use of the hazardous reagents hydrogen bromide and aniline).

**Related substances**: TLC replaced by LC in accordance with current policy.

**Assay**: modified to allow end-point determination by potentiometry.

**Impurities**: section added describing impurities controlled by LC.

**Orphenadrine citrate (1759)**

**Related substances**: reference to rotary evaporator has been deleted since other equipment or procedures may be used.

**Orphenadrine hydrochloride (1760)**

**Related substances**: reference to rotary evaporator has been deleted since other equipment or procedures may be used.

**Oxeladin hydrogen citrate (1761)**

**Related substances**: reference to rotary evaporator deleted since other equipment or procedure may be used.

**Oxolinic acid (1353)**

**Identification B**: sample preparation deleted.

**Assay**: reference to calomel electrode deleted following entry into force of EU Regulation 847/2012 restricting use of mercury in measuring devices.
Pancreas powder (0350)

*Lipolytic activity*: deletion of reference to calomel electrodes, following entry into force of EU Regulation 847/2012 restricting use of mercury in measuring devices.

Phenazine (0421)

*Assay*: addition of dilute acetic acid to make titration more robust.

Phentolamine mesilate (1138)

*Assay*: deletion of reference to calomel electrode, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Polysorbate 80 (0428)

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Potassium hydroxide (0840)

*Chlorides, Phosphates, Sulfates*: limits increased.

Povidone, iodinated (1142)

*Identification C*: deleted as it contained a reagent proscribed under the REACH Regulation (potassium dichromate solution); identification tests A and B together are considered specific enough to identify the substance.

Propylene glycol dicaprylocaprate (2122)

*Identification*: 2nd identification series added since the substance is used in hospital pharmacies; upper limit for viscosity increased.

*Saponification value*: lower limit decreased based on current batch data.

*Unsaponifiable matter*: in light of the manufacturing process, the level of unsaponifiable matter in the substance is very low, therefore the test is deleted.

Quinidine sulfate (0017)

*Definition*: degree of hydration added.

Quinine hydrochloride (0018)

*Definition*: degree of hydration added.

Quinine sulfate (0019)

*Definition*: degree of hydration added.

Risedronate sodium 2.5-hydrate (2572)

*Related substances test B*: injection of blank solution added; peaks eluting before risedronate disregarded.
Rivastigmine hydrogen tartrate (2630)

*Loss on drying:* test replaced by semi-micro determination of water.

Sodium amidotrizoate (1150)

*Assay:* deletion of the reference to the mercurous sulfate electrode, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Sodium hydroxide (0677)

*Chlorides, Sulfates:* limits increased.

Sodium nitroprusside (0565)

*Assay:* deletion of the reference to the mercurous sulfate electrode, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.

Sodium selenite pentahydrate (1677)

*Chlorides, Assay:* harmonised with the new monograph on *Sodium selenite* (2740).

Spirapril hydrochloride monohydrate (1766)

*Identification B:* sample preparation deleted.

*Identification C (chlorides):* to avoid use of potassium dichromate (test (b)) in accordance with REACH regulation, only test (a) is now prescribed.

Sucrose (0204)

*Identification B:* system suitability performed using reagents instead of CRSs.

Sugar spheres (1570)

*Identification A:* system suitability performed using reagents instead of CRSs.

Sulfacetamide sodium (0107)

*Definition:* updated to include the degree of hydration according to current Ph. Eur. policy on hydrates.

Theophylline-ethylenediamine hydrate (0301)

*Definition:* updated to include ‘a variable quantity of water’ according to current Ph. Eur. policy on hydrates.

Thiamine hydrochloride (0303)

*Solubility:* solubility in a non-polar solvent added.

*Related substances:* limit for unspecified impurities explicitly given; limits for specified impurities A, B, C and total updated; CRS for peak identification of impurities A, B and C introduced and also used for system suitability instead of unspecified impurity E.
Thiamine nitrate (0531)

**Solubility**: solubility in methanol deleted; solubility in a non-polar solvent added.

**Identification A**: reference spectrum replaced by CRS.

**Related substances**: limit for unspecified impurities explicitly given; limits for specified impurities A, B, C and total updated; CRS for peak identification of impurities A, B and C introduced and also used for system suitability instead of unspecified impurity E.

Thiamphenicol (0109)

**Assay**: reference to silver indicator electrode and mercurous sulfate reference electrode deleted following entry into force of EU Regulation 847/2012 restricting use of mercury in measuring devices.

Tribenoside (1740)

**Related substances**: as each individual impurity is quantified against external standards, calculation of total impurities is amended to take this into account.

Trypsin (0694)

**Assay**: deletion of the reference to calomel electrodes, following the entry into force of EU Regulation 847/2012 restricting the use of mercury in measuring devices.