Comments concerning revised texts published in Supplement 9.8

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the June 2018 session and published in Supplement 9.8.

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

2.2.32. Loss on drying

In view of its toxicity, diphosphorus pentoxide has been replaced by a molecular sieve.

The conditions of 'high vacuum', which were reported to be difficult to achieve with available instruments, are deleted.

Additional clarifications are introduced throughout the general chapter.

2.2.35. Osmolality

The general chapter has been completely rewritten and its structure updated. This general revision includes: an updated section on the principle; clearer guidance for the calibration procedure; an accuracy requirement for calibration.

2.5.32. Water: micro determination

Due to a discrepancy in the assigned water content of *sodium aminosalicylate dihydrate for equipment qualification CRS*, the CRS has been replaced by *amoxicillin trihydrate for performance verification CRS* for the evaporation technique.

2.6.20. Anti-A and anti-B haemagglutinins

Method B - direct method: clarification on the execution of the test on normal immunoglobulins with an IgG concentration lower than 25 g/L added.

2.7.16. Assay of pertussis vaccine (acellular)

The method for calculation of assay results has been revised in line with WHO recommendations to assure the quality, safety and efficacy of acellular pertussis vaccines.

The assay results can be expressed for each antigen either as the antibody geometric mean titre (GMT) obtained with the test vaccine in absolute terms (GMU assay), or as a ratio of this

value to the antibody GMT obtained with a reference vaccine examined in parallel (relative potency assay).

The test vaccine complies with the geometric mean unit (GMU) assay if, for each antigen, the antibody GMT is not less than an acceptance criterion based on historical data obtained with representative batches and approved by the competent authorities for the particular product. An internal control is used in the GMU assay to check consistency.

The test vaccine complies with the relative potency assay if, for each antigen, the ratio of the antibody GMT to the antibody GMT obtained with the reference vaccine is not less than an acceptance criterion based on historical data obtained with representative batches and approved by the competent authorities for the particular product.

A glossary has also been added.

2.8.12. Essential oils in herbal drugs

The general chapter has been completely rewritten. This general revision covers the addition of 1,2,4-trimethylbenzene and trimethylpentane as collector solvents. The use of 1,2,4-trimethylbenzene as collector solvent allows the omission of the blank distillation step, thereby eliminating the associated error.

2.9.10. Ethanol content

Method B: volumes of solutions to be transferred to injection vials added.

2.9.11. Test for methanol and 2-propanol

Method A: volumes of solutions to be transferred to injection vials added.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include new monograph published in Supplement 9.8.

VACCINES FOR HUMAN USE

Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed) (1931)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) (2764)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Diphtheria, tetanus, pertussis (acellular, component) and haemophilus type b conjugate vaccine (adsorbed) (1932)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Diphtheria, tetanus, pertussis (acellular, component) and hepatitis B (rDNA) vaccine (adsorbed) (1933)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed) (1934)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (2329)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2067)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2065)

Assay of the pertussis component: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Influenza vaccine (split virion, inactivated) (0158)

Production: the starting point for counting the number of passages to the working seed lot has been clarified, by introducing the notion of a candidate vaccine virus (i.e. approved virus isolate or reassorted virus supplied by WHO designated laboratories, or established by vaccine manufacturers).

Influenza vaccine (surface antigen, inactivated) (0869)

Production: the starting point for counting the number of passages to the working seed lot has been clarified, by introducing the notion of a candidate vaccine virus (i.e. approved

virus isolate or reassorted virus supplied by WHO designated laboratories, or established by vaccine manufacturers).

Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) (2149)

Production: the starting point for counting the number of passages to the working seed lot has been clarified, by introducing the notion of a candidate vaccine virus (i.e. approved virus isolate or reassorted virus supplied by WHO designated laboratories, or established by vaccine manufacturers).

Influenza vaccine (surface antigen, inactivated, virosome) (2053)

Production: the starting point for counting the number of passages to the working seed lots has been clarified, by introducing the notion of a candidate vaccine virus (i.e. approved virus isolate or reassorted virus supplied by WHO designated laboratories, or established by vaccine manufacturers).

Influenza vaccine (whole virion, inactivated) (0159)

Production: the starting point for counting the number of passages to the working seed lot has been clarified, by introducing the notion of a candidate vaccine virus (i.e. approved virus isolate or reassorted virus supplied by WHO designated laboratories, or established by vaccine manufacturers).

Influenza vaccine (whole virion, inactivated, prepared in cell cultures) (2308)

Production: the starting point for counting the number of passages to the working seed lot has been clarified, by introducing the notion of a candidate vaccine virus (i.e. approved virus isolate or reassorted virus supplied by WHO designated laboratories, or established by vaccine manufacturers).

Pertussis vaccine (acellular, component, adsorbed) (1356)

Assay: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

Pertussis vaccine (acellular, co-purified, adsorbed) (1595)

Assay: section revised to reflect change in calculation method of the assay of acellular pertussis vaccine (see revised general chapter *2.7.16. Assay of pertussis vaccine (acellular)* published in the same supplement).

VACCINES FOR VETERINARY USE

Avian infectious bursal disease vaccine (live) (0587)

Immunosuppression (section 2-4-3): in order to clarify that the vaccine strain is to be administered by the least safe route of vaccination, and to take into account vaccines not administered by eye-drop (for example administered by subcutaneous route), administration by eye-drop is now only indicated for the Hitchner B1 strain Newcastle disease vaccine (live).

Equine influenza vaccine (inactivated) (0249)

Following antigenic drift of equine influenza virus, the OIE Expert Surveillance Panel for equine influenza vaccine composition recommended that equine influenza vaccines should contain strains from both Florida clade 1 and clade 2 sublineages. In this context, a biological reference preparation (BRP) containing antibodies against an equine influenza equi-2 American lineage, Florida clade 2 strain has been established (BSP 134), adopted by the Ph. Eur. Commission and accepted as OIE-approved International Standard. The equine influenza subtype 2 American-like strain A/eq/Richmond/1/2007 (Florida clade 2 representative strain) horse antiserum BRP has been added to the list of BRPs for the test for immunogenicity.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Technetium (^{99m}Tc) mebrofenin injection (2393)

Radiochemical purity: relaxation of general requirement in line with currently approved products; introduction of limits for colloidal technetium-99m (impurity A) and for hydrophilic impurities.

SUTURES FOR VETERINARY USE

Linen thread, sterile, in distributor for veterinary use (0608)

Identification: identification method B is no longer performed by chemical tests, but by IR using attenuated total reflection (ATR) *(2.2.24)*; the main peaks are given with an indication of their intensity (strong, medium, weak).

Silk suture, sterile, braided, in distributor for veterinary use (0606)

Identification: identification method B is no longer performed by chemical tests, but by IR using attenuated total reflection (ATR) (*2.2.24*); the main peaks are given with an indication of their intensity (strong, medium, weak).

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Acacia (0307)

Identification B: *ethanol (96 per cent) R* used for microscopic examination.

Identification C, Glucose and fructose, Tragacanth: TLC replaced by HPTLC referring to general chapter *2.8.25. High-performance thin-layer chromatography of herbal drugs and herbal drug preparations*.

Agnus castus fruit dry extract (2309)

Definition: content limit modified to take account of approved products available on the market.

Alchemilla (1387)

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

Dog rose (1510)

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

Identification C: in the preparation of the reference solution, the volume is expressed using fewer significant figures.

Dwarf pine oil (2377)

Relative density, Optical rotation, Chromatographic profile: updated to include oil from Allgäu region.

Ginseng (1523)

Assay: ginsenoside Rb1 and ginsenoside Rg1 reagents replaced by corresponding CRSs; grades of solvents amended in accordance with Technical Guide (2015).

Juniper (1532)

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

Matricaria flower (0404)

Essential oil: *xylene R* replaced by *1,2,4-trimethylbenzene R* to eliminate the error resulting from the loss of xylene.

Total apigenin-7-glucoside: reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

Notoginseng root (2383)

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

Assay: ginsenoside Rb1 and ginsenoside Rg1 reagents replaced by corresponding CRSs; grades of solvents amended in accordance with Technical Guide (2015).

Saw palmetto extract (2579)

Acid value: sample size reduced to allow better handling with common laboratory equipment.

Senega root (0202)

Definition: species covered by monograph defined more precisely.

Identification: macroscopic and microscopic identifications updated and illustration of powdered herbal drug introduced; TLC replaced by HPTLC.

Tests: tests for extractable matter, loss on drying and foam index introduced.

Sweet orange oil (1811)

Chromatographic profile: improved GC introduced; lower limit for β-myrcene reduced to take account of current batch data.

HOMOEOPATHIC PREPARATIONS

Acidum succinicum for homoeopathic preparations (2824)

Identification B: following establishment of *succinic acid CRS* (batch 1) that has a melting point at 188.2 °C, the upper specification for the melting point has been increased from 187 °C to 189 °C.

MONOGRAPHS

Acacia, dried dispersion (0308)

Title, Definition, Identification A: revised to cover roller-dried material.

Identification B, Glucose and fructose, Tragacanth: TLC replaced by HPTLC referring to general chapter *2.8.25. High-performance thin-layer chromatography of herbal drugs and herbal drug preparations*.

Ascorbic acid (0253)

Impurity E: requirement remains unchanged but the numerical value of the limit has been corrected to take into account that the reagent used is oxalic acid dihydrate, whereas impurity E is the anhydrous form of oxalic acid.

Related substances: grades of solvents amended in accordance with Technical Guide (2015); in the preparation of reference solution (c), volumes are expressed using fewer significant figures.

Asparagine monohydrate (2086)

Identification: cross-reference to test for loss on drying added to identify monohydrate form.

Ninhydrin-positive substances: TLC replaced by LC test for related substances; specifications updated based on batch data.

Ammonium: reference solution revised.

Benzylpenicillin (procaine) monohydrate (0115)

Title: updated to include degree of hydration.

Definition: updated to indicate starting material is either benzylpenicillin sodium or benzylpenicillin potassium.

Content: expression of limits clarified.

Specific optical rotation: test deleted.

Related substances, Assay: updated to include improved LC method capable of identifying additional impurities and limits adapted to reflect current market situation; limit for 'any other impurity' lowered from 1 per cent to 0.2 per cent; identification of remaining impurities occurring at levels between 0.1 per cent and 0.2 per cent was not possible.

Water: sample size reduced.

Impurities: section updated.

Betadex (1070)

Definition: upper limit for content increased.

Characters: hygroscopicity added.

Related substances: quantitative expression of acceptance criteria introduced; reporting threshold and identification of peaks added; concentration of reference solution (b) decreased to correspond to limits; grades of solvents amended in accordance with Technical Guide (2015).

Residual solvents: resolution criterion deleted; repeatability requirement increased to maximum 10.0 per cent and clarified; head-space conditions completed; relative retentions stated.

Assay: number of injections for relative standard deviation (RSD) added.

Calcium pantothenate (0470)

Identification B: TLC replaced by LC for related substances.

Impurity A: TLC replaced by potentiometric titration covering impurity A and other aminocarboxylic acid impurities.

Related substances: LC test introduced.

Impurities: section added.

Carboplatin (1081)

Related substances: grades of solvents amended in accordance with Technical Guide (2015); limit added for unspecified impurities.

Silver, Soluble barium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests have been deleted as the relevant impurities are considered to originate from the production process.

Chlorprothixene hydrochloride (0815)

Identification E: centrifugation step added after addition of dilute nitric acid.

Related substances: column dimensions and flow rate adjusted; reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015); identification of impurities section introduced; system suitability test improved; limits updated based on the quality of currently approved products on the European market; limit for unspecified impurities introduced.

Impurities: section updated.

Desflurane (1666)

Antimony: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant impurity is considered to originate from the production process.

Doxazosin mesilate (2125)

Related substances: in preparation of reference solution (c), volumes expressed using fewer significant figures; reagent used to describe stationary phase modified; concentration of phosphoric acid in mobile phases A and B decreased; identification of impurities subsection introduced.

Egg phospholipids for injection (2315)

Identification B, Assay (LC-ELSD): information that the peaks due to lysophosphatidylcholine and sphingomyelin could elute as 1 or 2 peaks added; dilution of the test solution is now permitted if saturation of the peak due to phosphatidylcholine is observed; in the preparation of reference solution (g), the volumes are expressed using fewer significant figures due to the qualitative use of this solution; last 2 steps of gradient corrected.

Erythritol (1803)

Related substances: in the preparation of reference solution (d), volume is expressed using fewer significant figures due to the qualitative use of this solution; resolution is expressed using more significant figures; internal diameter of column is corrected.

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Assay: usual wording used for calculation.

Etanercept (2895)

Related proteins: peak separation criterion for system suitability adjusted.

Potency: preparation of reference solutions amended and concentration expressed in IU/mL.

Ethacridine lactate monohydrate (1591)

Second identification: to avoid the use of cobalt chloride (former test C), the 2nd identification series has been updated; only the reaction of lactates and a new TLC method with 3 detections are now described.

Related substances: reagent used to describe stationary phase modified.

Filgrastim concentrated solution (2206)

Definition: reference to 174-amino acid isoform of human G-CSF introduced; wording aligned with that of monograph *Filgrastim injection (2848).*

Fingolimod hydrochloride (2988)

Water: limit increased to 0.3 per cent.

Flupentixol dihydrochloride (1693)

Definition: upper and lower content limits of flupentixol dihydrochloride modified.

Appearance of solution: test for degree of coloration of liquids (*2.2.2*) replaced by more accurate absorbance test (*2.2.25*).

Related substances, Impurity F: former tests replaced by a single, more sensitive LC method; limits updated based on the quality of currently approved products on the European market. An isocratic step before the start of the gradient programme has not been introduced as this negatively affects the selectivity of the method. The correction factors for coeluting impurities C and I are 0.4 and 2.0 respectively, therefore a correction factor of 2.0 is applied to calculate their sum.

Assay of (Z)-isomer: grade of solvent amended in accordance with Technical Guide (2015); run time, identification of peaks and relative retention sections introduced; second statement in former results section deleted.

Impurities: impurity D deleted as it is not detected in batches; impurity F now listed as impurities H and I.

Fructose (0188)

Barium, Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests are deleted as the relevant elemental impurities are not considered pertinent in view of state-of-the-art production processes.

Glucosamine sulfate potassium chloride (2708)

Sulfated ash: addition of specific instructions requiring an initial ashing for 2 h with no addition of sulfuric acid between any re-ignitions performed.

Glucosamine sulfate sodium chloride (2447)

Sulfated ash: addition of specific instructions requiring an initial ashing for 2 h with no addition of sulfuric acid between any re-ignitions performed.

Heparins, low-molecular-mass (0828)

Identification C: method for calibrating the chromatographic system using the ratio of refractive index to UV absorbance has been replaced by a more reproducible and technically easier calibration method using a Broad Standard Table (Broad Standard Table method); sodium sulfate has been replaced by ammonium acetate as the eluent buffer in order to improve the chromatographic separation.

Hydrocortisone acetate (0334)

Related substances: concentration of reference solution (c) now aligned with concentration of test solution (a); grade of solvents amended in accordance with Technical Guide (2015).

myo-Inositol (1805)

Related substances: tolerance for column temperature added; resolution expressed using more significant figures; grade of solvent amended in accordance with Technical Guide (2015).

Barium, Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, these tests are deleted as the relevant elemental impurities are not considered pertinent in view of state-of-the-art production processes.

Isomalt (1531)

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Lactitol monohydrate (1337)

Related substances: resolution expressed using more significant figures.

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Lactulose (1230)

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Related substances: in the preparation of reference solution (c), volume is expressed using fewer significant figures due to the qualitative use of the solution.

Lactulose, liquid (0924)

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Related substances: in the preparation of reference solution (d), the volume is expressed using fewer significant figures due to the qualitative use of this solution.

Loperamide hydrochloride (0929)

Related substances: limits updated to reflect quality of currently approved products on the European market; reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

Macrogol lauryl ether (1124)

Definition: definition reworded to specify that only linear fatty alcohols are covered.

Characters: section modified to describe differences presented by macrogol lauryl ethers with 9 units of ethylene oxide per molecule.

Identification: tests E (for products with 3 to 5 units of ethylene oxide per molecule) and F (for products with 9 to 23 units of ethylene oxide per molecule) introduced.

Sulfated ash: test introduced to replace test for total ash.

Macrogol stearate (1234)

Melting point, Hydroxyl value, Saponification value: specifications added for product containing 32 units of ethylene oxide per molecule and specifications revised for product containing 6 units of ethylene oxide per molecule, based on current batch data; Table 1234.-1 updated accordingly.

Acid value: limit slightly increased to include product containing 32 units of ethylene oxide per molecule, based on current batch data.

Magnesium pidolate (1619)

Related substances: reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests has been deleted as the relevant elemental impurity is considered to originate from the production process.

Maltitol (1235)

Identification A: description of sample preparation deleted.

Related substances: resolution expressed using more significant figures; in the preparation of reference solution (d), volume is expressed using fewer significant figures due to the qualitative use of this solution; grade of solvent amended in accordance with Technical Guide (2015).

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Assay: usual wording indicated for calculation.

Maltitol, liquid (1236)

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Water: anhydrous grade of formamide included.

Assay: resolution expressed using more significant figures; in the preparation of reference solution (c), volume expressed using fewer significant figures due to the qualitative use of this solution; grade of solvent amended in accordance with Technical Guide (2015); usual wording indicated for calculation.

Mannitol (0559)

Nickel: in line with the Ph. Eur. implementation strategy for ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Related substances: grade of solvent amended in accordance with Technical Guide (2015).

Assay: usual wording introduced for calculation.

Mefenamic acid (1240)

Related substances: in the preparation of reference solution (b), the volumes are expressed using fewer significant figures due to the qualitative use of this solution; grades of solvents amended in accordance with Technical Guide (2015).

Copper: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Meglumine (2055)

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Mesalazine (1699)

Appearance of solution, Chlorides: unnecessary use of volumetric solutions avoided.

Impurities A and C: new reference solution (b) introduced with concentration of impurity C corresponding to specification of impurity C; in preparation of new reference solution (d), volumes expressed using fewer significant figures; reagent used to describe stationary phase modified.

Impurity K: reagent used to describe stationary phase modified.

Related substances: unnecessary use of volumetric solutions avoided; in preparation of reference solutions (b) and (c), volumes expressed using fewer significant figures.

Methyl salicylate (0230)

Content: upper limit increased.

Identification: section split in 2 series; IR introduced (1st series) and 2nd series consists of former tests A and B.

Relative density: specification modified to reflect quality of currently approved products on the European market.

Related substances: test introduced to cover 10 impurities (acidic impurities such as 2-hydroxybenzoic acid, 4-hydroxyisophthalic acid and 4-hydroxybenzoic acid are covered by the test for acidity).

Impurities: section added.

Methylthioninium chloride hydrate (1132)

Title, Definition: modified in accordance with current policy and Technical Guide (2015).

Identification: identification tests by TLC and UV spectrophotometry replaced by infrared absorption spectrophotometry.

Related substances: in preparation of reference solution (c), volume expressed using fewer significant figures; reagent used to describe stationary phase modified; column temperature added and grade of acetonitrile in mobile phase B amended in accordance with Technical Guide (2015).

Elemental impurities: since the test now refers to general chapter *2.4.20. Determination of elemental impurities*, thus allowing the use of any method that fulfils the requirements described in the general chapter itself, the atomic emission spectrometry method has been deleted.

Stricter limits than those calculated by applying option 2A of the ICH Q3D guideline (the corresponding medicinal product being approved for parenteral use with a maximum daily dose of 0.5 g) are retained for cadmium, chromium, copper, mercury, molybdenum, nickel and tin. The substance is a chelating agent and part of its therapeutic activity is based on this property. Therefore it cannot be excluded that wider limits for these elemental impurities (thus allowing the presence of higher amounts of certain metal complexes) would impact the efficacy of the drug substance.

Moxifloxacin hydrochloride (2254)

Production: section deleted as test for enantiomeric purity added.

Identification: reference to specific optical rotation replaced by reference to enantiomeric purity.

Specific optical rotation: test replaced by LC test for enantiomeric purity.

Enantiomeric purity: LC test introduced.

Related substances: reagent used to describe stationary phase modified; system suitability test simplified; 2 additional impurities covered by current method; limits updated based on quality of currently approved products on the European market.

Impurities: section updated.

Oxaliplatin (2017)

Impurity D: reagent used to describe stationary phase modified.

Related substances: grades of solvents amended in accordance with Technical Guide (2015); reagents used to describe stationary phases modified.

Silver: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Oxfendazole for veterinary use (1458)

Definition: relative molecular mass updated.

Related substances: reference solution (b) *in situ* degradation of oxfendazole made explicit; former reference solution (c) replaced by reference solutions (c) and (d) containing 1 impurity each; description of stationary phase modified; run time extended to allow elution of impurity A; Identification of impurities section added; retention time of oxfendazole and relative retention times of impurities A to D updated.

Parnaparin sodium (1252)

Definition: in accordance with *Heparins, low-molecular-mass (0828)*, low molecular mass heparins are obtained by fractionation or depolymerisation of heparin of natural origin that complies with the monograph *Heparin sodium (0333)* or *Heparin calcium (0332)* (whichever is appropriate), unless otherwise justified and authorised. Since the scope of monographs on unfractionated heparin is restricted to heparin of porcine origin, the scope of the monograph *Parnaparin sodium* has been corrected accordingly.

Copper: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Prazosin hydrochloride (0856)

Related substances: reagent used to describe stationary phase modified; limits updated to reflect quality of currently approved products on the European market; explicit criterion for the unspecified impurities introduced; section aligned with requirements in general monograph *Substances for pharmaceutical use (2034)*.

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Impurities: section updated to include specified and other detectable impurities.

Prochlorperazine maleate (0244)

Identification: former tests A and D deleted.

Related substances: TLC replaced by LC covering 4 new impurities.

Impurities: section added.

Ramipril (1368)

Palladium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Related substances: reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

Sodium ascorbate (1791)

Impurity E: the requirement remains unchanged but the numerical value of the limit has been corrected to take into account that the reagent used is oxalic acid dihydrate, whereas impurity E is the anhydrous form of oxalic acid.

Related substances: grades of solvents amended in accordance with Technical Guide (2015); in the preparation of reference solution (c), volumes are expressed using fewer significant figures.

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Sorbitol (0435)

Identification C: plate without binder now prescribed as for *Mannitol (0559)*.

Related substances: in the preparation of reference solution (d), volume is expressed using fewer significant figures due to the qualitative use of this solution; grade of solvent amended in accordance with Technical Guide (2015).

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Water: anhydrous grade of formamide included.

Assay: usual wording indicated for calculation.

Sorbitol, liquid (crystallising) (0436)

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Assay: in the preparation of reference solution (b), volume is expressed using fewer significant figures due to the qualitative use of this solution; grade of solvent amended in accordance with Technical Guide (2015); usual wording indicated for calculation.

Sorbitol, liquid (non-crystallising) (0437)

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is not considered pertinent in view of state-of-the-art production processes.

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Assay: in the preparation of reference solution (b), volume is expressed using fewer significant figures due to the qualitative use of this solution; grade of solvent modified in accordance with Technical Guide (2015); usual wording indicated for calculation.

Sorbitol, liquid, partially dehydrated (2048)

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process.

Assay: in the preparation of reference solution (b), volume is expressed using fewer significant figures due to the qualitative use of this solution; grade of solvent amended in accordance with Technical Guide (2015); usual wording indicated for calculation.

Soya phospholipids for injection (2316)

Identification A (TLC): retardation factors of the spots due to phosphatidylethanolamine and *N*-acyl-phosphatidylethanolamine corrected.

Identification B, Assay (LC-ELSD): information that the peak due to *N*-acyl-phosphatidylethanolamine could elute as 1 or 2 peaks added; composition of the solvent mixture modified; dilution of the test solution is now permitted if saturation of the peak due to phosphatidylcholine is observed; in the preparation of reference solution (g), the volumes are expressed using fewer significant figures due to the qualitative use of this solution.

Spironolactone (0688)

Related substances: grades of solvents amended in accordance with Technical Guide (2015).

Chromium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Sulfobutylbetadex sodium (2804)

Content: limits enlarged to take account of the various degrees of substitution covered by the monograph.

Assay: expression for calculation modified to refer to sulfobutylbetadex sodium instead of its molecular formula.

Teicoplanin (2358)

Chemical structure: parent structure corrected and table updated to include structures of 2 minor components (teicoplanins $A_{2\text{-}1a}$ and $A_{2\text{-}1b}$); full structures of other teicoplanin-like minor components with relative retentions 1.25, 1.30 and 1.38 not yet confirmed.

Definition, Identification: updated to include 2 minor components (teicoplanins $A_{2\text{-}1a}$ and $A_{2\text{-}1b}$).

Composition: text updated with information on relative retentions for minor components; equations for calculation of content reformatted and revised; limits for composition revised in accordance with EMA assessment report EMA/194668/2013.

Related Substances: definition of teicoplanin-like related substances included; instruction for identification of teicoplanin-like and non-teicoplanin-like peaks included; limits for known teicoplanin-like related substances, individual non-teicoplanin-like impurities and total non-teicoplanin-like impurities introduced in accordance with EMA assessment report EMA/194668/2013, and taking into account available batch data for currently marketed products in Europe.

Bacterial endotoxins: test removed in accordance with Ph. Eur. policy of February 2015 (see Pharmeuropa Online, Technical information).

Tolfenamic acid (2039)

Related substances: reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

Copper: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities the test has been deleted as the relevant impurity is considered to originate from the production process.

Trandolapril (2245)

Related substances: grades of solvents amended in accordance with Technical Guide (2015); wording of unspecified impurities aligned with the requirements of general chapter *5.10. Control of impurities in substances for pharmaceutical use*.

Palladium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Valaciclovir hydrochloride (1768)

Identification: cross-reference to test for water introduced in line with policy on hydrates.

Related substances: grades of solvents amended in accordance with Technical Guide (2015); reagent used to describe stationary phase modified; specifications for impurities H and J revised in accordance with available batch data.

Palladium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Valaciclovir hydrochloride hydrate (2751)

Title (English only): updated to align with policy on hydrates.

Related substances: grades of solvents amended in accordance with Technical Guide (2015); specifications for impurities H and P revised in accordance with available batch data.

Palladium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

Vancomycin hydrochloride (1058)

Definition: means of production restricted to certain strains of *Amycolatopsis orientalis*.

Characters: solubility updated.

Appearance of solution: limit for absorption at 370 nm introduced, based on available batch data.

Vancomycin B and related substances: improved LC method capable of separating a number of impurities introduced; limit for vancomycin B revised and limits introduced for a number of newly specified impurities, based on available batch data.

Bacterial endotoxins: test deleted, based on Ph. Eur. policy.

Labelling: section included.

Impurities: section updated.

Xylazine hydrochloride for veterinary use (1481)

Solution S: requirement to prepare *carbon dioxide-free water R* from *distilled water R* deleted in accordance with Technical Guide (2015).

Impurity A: test deleted as impurity A now controlled by test for related substances.

Related substances: reference solutions modified; grade of solvents amended in accordance with Technical Guide (2015); equilibration step deleted; and limits updated based on the quality of currently approved products on the European market.

Impurities: section updated.