Comments concerning revised texts published in Supplement 9.6

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November 2017 session and published in Supplement 9.6.

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

2.2.9. Capillary viscometer method

The chapter has been completely reviewed and a section on calibration has been added.

2.2.17. Drop point

References to mercury thermometer deleted.

2.2.28. Gas chromatography

General revision to reflect current practice.

2.2.29. Liquid chromatography

General review of the text.

Detectors: MALS detector added.

2.2.30. Size-exclusion chromatography

Principle: wording aligned with general chapter *2.2.46. Chromatographic separation techniques*.

Equipment: several detectors added, including a MALS detector.

2.2.38. Conductivity

The general chapter has undergone a complete revision and corresponds to Stage 5B within the Pharmacopoeial harmonisation process (Ph. Eur., JP, USP).

2.3.2. Identification of fatty oils by thin-layer chromatography

Method A (Figure 2.3.2.-1): chromatogram of hydrogenated arachis oil added.

2.8.13. Pesticide residues

Limit for pendimethalin increased from 0.1 mg/kg to 0.5 mg/kg.

3.1.1.1. Materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components

Production. In addition to di(2-ethylhexyl)phthalate (plastic additive 01), 4 additional plasticisers have been included:

- cyclohexane 1,2-dicarboxylic acid, diisononyl ester (plastic additive 24);
- butyryl tri-*n*-hexyl citrate (plastic additive 25);
- tris(2-ethylhexyl) trimellitate (plastic additive 26);
- bis(2-ethylhexyl) terephthalate (plastic additive 27).

A paragraph has also been added to explain that the selection of the composition of the materials and additives must be suitable for the intended use.

Identification B: identification of plastic additive 01 by IR absorption spectrophotometry has been replaced by a cross-reference to the test for plastic additives 01, 24, 25, 26 and 27 by GC coupled with mass spectrometry.

Plastic additives 01, 04 and 05: plastic additive 01 is now controlled by GC coupled with mass spectrometry, which is also applicable to the 4 additional plasticisers (plastic additives 24, 25, 26 and 27) in the new test for plastic additives 01, 24, 25, 26 and 27; plastic additives 04 and 05 are still controlled by TLC in the test for plastic additives 04 and 05.

3.1.1.2. Materials based on plasticised poly(vinyl chloride) for tubing used in sets for the transfusion of blood and blood components

Production. In addition to di(2-ethylhexyl)phthalate (plastic additive 01), 4 additional plasticisers have been included:

- cyclohexane 1,2-dicarboxylic acid, diisononyl ester (plastic additive 24);
- butyryl tri-*n*-hexyl citrate (plastic additive 25);
- tris(2-ethylhexyl) trimellitate (plastic additive 26);
- bis(2-ethylhexyl) terephthalate (plastic additive 27).

The 5 plasticisers and their limits are given in the new section Additives.

A paragraph has also been added to explain that the selection of the composition of the materials and additives must be suitable for the intended use.

Identification B: identification of plastic additive 01 by IR absorption spectrophotometry has been replaced by a cross-reference to the test for plastic additives 01, 24, 25, 26 and 27 by GC coupled with mass spectrometry.

Plastic additive 01: plastic additive 01 is now controlled by GC coupled with mass spectrometry, which is also applicable to the 4 additional plasticisers (plastic additives 24, 25, 26 and 27) in the new test for plastic additives 01, 24, 25, 26 and 27.

3.1.13. Plastic additives

Definition, General requirements: sections added to provide additional information regarding the quality of plastic additives to be used for materials and containers for pharmaceutical use.

List: 4 additional plasticisers have been included:

- cyclohexane 1,2-dicarboxylic acid, diisononyl ester (plastic additive 24);
- butyryl tri-*n*-hexyl citrate (plastic additive 25);
- tris(2-ethylhexyl) trimellitate (plastic additive 26);
- bis(2-ethylhexyl) terephthalate (plastic additive 27).

To avoid duplicating reference numbers for each substance, the plastic material registration numbers (PM RNs) have been deleted.

3.1.14. Materials based on plasticised poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion

Identification B: identification of plastic additive 01 by IR absorption spectrophotometry replaced by a cross-reference to the test for plastic additive 01 by GC coupled with mass spectrometry.

Plastic additives 01, 04 and 05: plastic additive 01 now controlled by GC coupled with mass spectrometry in the test for plastic additive 01; plastic additives 04 and 05 are still controlled by TLC in the test for plastic additives 04 and 05.

3.2.1. Glass containers for pharmaceutical use

Hydrolytic resistance: additional details included concerning autoclaving process with respect to equipment and handling; procedure for cleaning containers to be tested revised to improve reproducibility; instructions and specifications added to take small containers into account.

3.2.3. Sterile plastic containers for human blood and blood components

Tests: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

3.2.4. Empty sterile containers of plasticised poly(vinyl chloride) for human blood and blood components

Definition: reference to general chapter *3.1.1* corrected to *3.1.1.1*.

Reference solution: in accordance with the revision of general chapter *3.1.1.1*, *water for injections R* has been replaced with *water R*, as sterilised water for injections is considered unsuitable for testing purposes.

Acidity or alkalinity: cross-reference to general chapter *3.2.3* added for solution S_2; ‘capacity’ changed to ‘value’.

Absorbance: cross-reference to general chapter *2.2.3* added for solution S_2.

Oxidisable substances: test renamed Reducing substances; ‘quantity’ changed to ‘volume’; ‘capacity’changed to ‘value’.

Extractable di(2-ethylhexyl)phthalate: replaced with Plastic additives 01, 24, 25, 26 and 27 (GC coupled with mass spectrometry test) to identify and quantify the 5 plastic additives 01 (di(2-ethylhexyl)phthalate), 24, 25, 26 and 27; the following 4 additional plasticisers have been included:

- cyclohexane 1,2-dicarboxylic acid, diisononyl ester (plastic additive 24);
- butyryl tri-*n*-hexyl citrate (plastic additive 25);
- tris(2-ethylhexyl) trimellitate (plastic additive 26);
- bis(2-ethylhexyl) terephthalate (plastic additive 27).

Ammonium: test deleted as, according to information available, ammonium is no longer used during the polymerisation steps.

Packaging: section renamed Storage.

3.2.5. Sterile containers of plasticised poly(vinyl chloride) for human blood containing anticoagulant solution

Definition: reference to general chapter *3.1.1* corrected to *3.1.1.1*.

Spectrophotometric examination: test renamed Absorbance.

Extractable di(2-ethylhexyl)phthalate: replaced with Plastic additives 01, 24, 25, 26 and 27 (GC coupled with mass spectrometry test) to identify and quantify the 5 plastic additives 01 (di(2-ethylhexyl)phthalate), 24, 25, 26 and 27 as described in general chapter *3.2.4*; the following 4 additional plasticisers have been included:

- cyclohexane 1,2-dicarboxylic acid, diisononyl ester (plastic additive 24) ;
- butyryl tri-*n*-hexyl citrate (plastic additive 25) ;
- tris(2-ethylhexyl) trimellitate (plastic additive 26) ;
- bis(2-ethylhexyl) terephthalate (plastic additive 27).

Packaging and labelling: section renamed and split into Storage and Labelling.

5.8. Pharmacopoeial harmonisation

Information modified for 5 excipients and added for 1 general chapter (*2.2.38*) and 1 excipient.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include new monographs published in Supplement 9.6.

GENERAL MONOGRAPHS

Allergen products (1063)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Immunosera for human use, animal (0084)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Products of fermentation (1468)

Due to the public health risk associated with histamine contamination (see for example: Public Health Risks of Histamine and other Biogenic Amines from Fish and Fishery Products, Meeting report, 23-27 July 2012 FAO headquarters, Rome Italy), further requirements related to the quality of raw materials were added to the Raw materials section.

The present monograph was adopted by the European Pharmacopoeia Commission by correspondence on 12 January 2018 and implemented on 1 April 2018.

DOSAGE FORMS

Granules (0499)

Definition: definition revised to cover new Standard Term ‘Granules in sachet’.

Pressurised pharmaceutical preparations (0523)

Definition: adapted to existing Standard Terms; depending on the intended use, the preparation is sterile.

Requirements for pressurised pharmaceutical preparations: section deleted, content moved to Definition and new Production section.

Production: section added.

Sterility: test added.

Sticks (1154)

Production, Tests: uniformity requirements deleted from Production section and now considered under Tests.

VACCINES FOR HUMAN USE

Anthrax vaccine for human use (adsorbed, prepared from culture filtrates) (2188)

Tests: test for abnormal toxicity deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

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

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Haemophilus type b conjugate vaccine (1219)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Hepatitis A (inactivated, adsorbed) and typhoid polysaccharide vaccine (2597)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (adsorbed) (1526)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Hepatitis A vaccine (inactivated, adsorbed) (1107)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Hepatitis A vaccine (inactivated, virosome) (1935)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Hepatitis B vaccine (rDNA) (1056)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Human papillomavirus vaccine (rDNA) (2441)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Influenza vaccine (split virion, inactivated) (0158)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Influenza vaccine (surface antigen, inactivated) (0869)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

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

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

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

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Influenza vaccine (whole virion, inactivated) (0159)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

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

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

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

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Measles, mumps, rubella and varicella vaccine (live) (2442)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Measles vaccine (live) (0213)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Meningococcal group C conjugate vaccine (2112)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Meningococcal polysaccharide vaccine (0250)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Mumps vaccine (live) (0538)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Pneumococcal polysaccharide conjugate vaccine (adsorbed) (2150)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Pneumococcal polysaccharide vaccine (0966)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Poliomyelitis vaccine (inactivated) (0214)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Rabies vaccine for human use prepared in cell cultures (0216)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Rubella vaccine (live) (0162)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Shingles (herpes zoster) vaccine (live) (2418)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Smallpox vaccine (live) (0164)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Tick-borne encephalitis vaccine (inactivated) (1375)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Typhoid polysaccharide vaccine (1160)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Typhoid vaccine (0156)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Varicella vaccine (live) (0648)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Yellow fever vaccine (live) (0537)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Akebia stem (2472)

Identification A: updated.

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

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

Bilberry fruit, dried (1588)

Identification A: updated to allow better discrimination from other herbal drugs.

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

Foreign matter: test for adulteration with *Sambucus nigra* L. introduced.

Bilberry fruit, fresh (1602)

Identification A: updated to allow better discrimination from other herbal drugs.

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

Foreign matter: test for adulteration with *Sambucus nigra* L. introduced.

Fenugreek (1323)

Characters: section deleted.

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

Garlic powder (1216)

Definition: adapted to reflect herbal drug available on market.

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

Isatis root (2566)

Identification A: description updated.

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

Assay: reagent used to describe stationary phase modified and grades of solvents amended in accordance with the Technical Guide (2015).

Milk thistle dry extract, refined and standardised (2071)

Water: test for loss on drying replaced by determination of water (*2.5.12*).

White horehound (1835)

Characters: section deleted.

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

Assay: *marrubiin R* replaced by *marrubiin CRS*; grades of solvents amended in accordance with the Technical Guide (2015).

MONOGRAPHS

Amikacin sulfate (1290)

Assay: *amikacin CRS* with appropriate conversion factor introduced for calculation of content.

Amisulpride (1490)

Related substances: *dilute sulfuric acid R* now used directly to adjust pH of the mobile phase and grades of solvents amended in accordance with the Technical Guide (2015).

Ammonio methacrylate copolymer (type A) (2081)

Identification: reference spectrum replaced by CRS.

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

Assay: *anhydrous formic acid R* and *acetic anhydride R* replaced by a solution of *copper acetate R* in *glacial acetic acid R* to improve method robustness.

Ammonio methacrylate copolymer (type B) (2082)

Identification: reference spectrum replaced by CRS.

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

Assay: *anhydrous formic acid R* and *acetic anhydride R* replaced by a solution of *copper acetate R* in *glacial acetic acid R* to improve method robustness.

Aprotinin (0580)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Pyroglutamyl-aprotinin and related compounds; Aprotinin oligomers: grades of solvents amended in accordance with the Technical Guide (2015).

Aprotinin concentrated solution (0579)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Pyroglutamyl-aprotinin and related compounds; Aprotinin oligomers: grades of solvents amended in accordance with the Technical Guide (2015).

Arachis oil, hydrogenated (1171)

Identification: reference to test for composition of fatty acids moved to first identification series; identification of fatty oils by TLC moved to second identification series.

Arachis oil, refined (0263)

Identification: reference to test for composition of fatty acids added to first identification series; identification of fatty oils by TLC moved to second identification series.

Benzylpenicillin (benzathine) tetrahydrate (0373)

Title: updated to include degree of hydration.

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

Content: limits adapted and expressed without correction for dispersing or suspending agents.

Related substances, Assay: updated to include improved LC method capable of identifying additional impurities; adaptation of limits to reflect current market situation.

Water: sample size reduced.

Impurities: section updated.

Botulinum toxin type A for injection (2113)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Botulinum toxin type B for injection (2581)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Calcifediol monohydrate (1295)

Title: degree of hydration added.

***Content*:** lower limit updated following modification of limit for total impurities.

Related substances: relative retentions corrected; limits updated; CRS introduced to identify specified impurity D; reagent used to describe stationary phase modified; grades of solvents amended in accordance with the Technical Guide (2015).

Water: operating conditions added and suitable reagent stated in Knowledge database.

Assay: repeatability requirement omitted as it complies with requirement given in general chapter *2.2.46. Chromatographic separation techniques*.

Calcipotriol (2011)

Related substances test B: CRS for system suitability now used; grades of solvents amended in accordance with the Technical Guide (2015); reagent used to describe stationary phase modified.

Calcipotriol monohydrate (2284)

Related substances test B: CRS for system suitability now used; grades of solvents amended in accordance with the Technical Guide (2015); reagent used to describe stationary phase modified.

Calcium hydrogen phosphate (0981)

This text corresponds to Revision 2, Stage 5B within the Pharmacopoeial harmonisation process (Ph. Eur., JP, USP).

Content, Loss on ignition: limits modified.

Acid-insoluble substances, Chlorides, Sulfates: clarification added.

Carbonates: sample size and volume of acid increased.

Cellulose, microcrystalline (0316)

This text corresponds to Revision 2, Stage 5B within the Pharmacopoeial harmonisation process (Ph. Eur., JP, USP).

Identification: identification test by IR absorption spectrophotometry added.

Chlorobutanol (0382)

Identification: IR introduced to replace former identification tests A, B and C.

Impurities A and B: test added to control 2 new impurities.

Assay: end-point determination by colour indicator replaced by potentiometry, thereby also avoiding the use of dibutyl phthalate (REACH).

Impurities: section introduced.

Chlorobutanol hemihydrate (0383)

Identification: IR introduced to replace former identification tests A, B and C.

Impurities A and B: test added to control 2 new impurities.

Assay: end-point determination by colour indicator replaced by potentiometry, thereby also avoiding the use of dibutyl phthalate (REACH).

Impurities: section introduced.

Cholecalciferol concentrate (oily form) (0575)

Identification: TLC in Identification A deleted as, depending on the vegetable oil used for preparation, the method was not always applicable; identification tests B and C renamed accordingly; 2nd identification series deleted as substance not used in pharmacies.

Cinchocaine hydrochloride (1088)

Related substances: TLC replaced by LC, specifications updated.

Colistin sulfate (0320)

Structure: updated to include polymyxin components E4, E2-Val, E1-Nva, E6, E2-I and 2,3-dehydro E1.

Definition: updated to restrict production to the use of certain strains of *Bacillus polymyxa* var. *colistinus*.

Specific optical rotation: test removed as quality adequately controlled by tests for composition and related substances.

Composition: modified method introduced with new limits based on current market quality.

Related substances: limits for any other and total impurities revised based on current market quality.

Impurities: section added.

Cystine (0998)

Ninhydrin-positive substances: solution A modified to replace *dilute hydrochloric acid R1* by a 10.3 g/L solution of *hydrochloric acid R* to allow complete dissolution of the substance.

Cytarabine (0760)

Identification: tests A and C deleted since IR absorption spectrophotometry sufficiently specific.

Related substances: TLC replaced by LC; list of impurities and limits updated.

Dihydrostreptomycin sulfate for veterinary use (0485)

Production: section deleted as the test for abnormal toxicity (*2.6.9*) was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Related substances: reagent used to describe stationary phase modified and pH adjustement of mobile phase clarified.

Dihydrotachysterol (2014)

Related substances: ChromPack CP-Ecospher 4 PAH column found suitable during monograph development is no longer available, a YMC PAH column with a 3 µm particle size instead of 4 µm can be used instead and the description of the stationary phase has been updated accordingly; grades of solvents amended in accordance with the Technical Guide (2015).

Disodium phosphate dodecahydrate (0118)

Water: method (*2.5.12*) replaced by loss on drying.

Monosodium phosphate, Assay: blank determination added and used in the calculation.

Ebastine (2015)

Identification: reference spectrum replaced by CRS.

Related substances: LC method revised to reduce run time.

Impurities: impurity H added to transparency list; all impurities now listed as unspecified impurities.

Erythropoietin concentrated solution (1316)

Peptide mapping: reagent used to describe stationary phase modified, and grades of solvents amended in accordance with the Technical Guide (2015).

Dimers and related substances with molecular masses greater than that of erythropoietin: former name of test modified; method updated to apply the normalisation procedure, and to include *erythropoietin for SEC system suitability CRS* and new chromatographic column requirements.

Ethosuximide (0764)

Impurities: section updated; impurities A and B now unspecified.

Glycerol (0496)

Second identification: series updated to avoid the use of potassium dichromate (test C); relative density now added.

Glycerol (85 per cent) (0497)

Second identification: series updated to avoid the use of potassium dichromate (test C); relative density now added.

Granisetron hydrochloride (1695)

Related substances: for the calculation of the symmetry factor in the system suitability test, reference is made to the chromatogram obtained with reference solution (a); grades of solvents amended in accordance with the Technical Guide (2015).

Griseofulvin (0182)

Production: section deleted as the test for abnormal toxicity was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Haemodialysis, solutions for (0128)

Aluminium: qualitative test method replaced with atomic absorption spectrometry (AAS) (quantitative test); the same limit as required for *Solutions for haemofiltration and haemodiafiltration (0861)* and for *Solutions for peritoneal dialysis (0862)* has been applied.

Total chloride: assay method using dibutyl phthalate reagent (included in Annex XIV of REACH) replaced with potentiometric titration.

Haemofiltration and haemodiafiltration, solutions for (0861)

Aluminium: qualitative test method replaced with atomic absorption spectrometry (AAS) (quantitative test).

Total chloride: assay method using dibutyl phthalate reagent (included in Annex XIV of REACH regulation) replaced with potentiometric titration.

Hypromellose (0348)

This text corresponds to Revision 2, Stage 5B within the Pharmacopoeial harmonisation process (Ph. Eur., JP, USP).

Assay: chromatographic conditions modified to replace the packed column by a capillary column.

Kanamycin acid sulfate (0033)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Kanamycin monosulfate (0032)

CAS number: added.

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Levocarnitine (1339)

Related substances: limit for total impurities and disregard limit added; limit for impurity A lowered based on batch data; for system suitability, preparation of reference solution (c) has been revised and the resolution factor increased to 1.5. Grades of solvents amended in accordance with the Technical Guide (2015).

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

Lidocaine hydrochloride monohydrate (0227)

Title: degree of hydration specified.

Related substances: statement about not disregarding the peak due to impurity A added, and section Identification of impurities introduced.

Mepivacaine hydrochloride (1242)

Characters: statement on polymorphism added.

Identification: recrystallisation step added in identification A due to the presence of different crystalline forms; ether replaced by 1,1-dimethylethyl methyl ether in identification B; identification by melting point deleted.

Related substances: identification of impurities and relative retention introduced, and limits updated; explicit acceptance criterion for unspecified impurities introduced and disregard limit modified to be in line with the general monograph *Substances for Pharmaceutical Use (2034)*; reagent used to describe stationary phase modified.

Impurity A: colour test replaced by GC with a tighter limit.

Methacrylic acid - ethyl acrylate copolymer (1:1) (1128)

IR identification: clarification that 2 distinct CRSs are used for types A and B.

Viscosity (for type B): quantity of solvent increased.

Ethyl acrylate and methacrylic acid: grades of solvents amended in accordance with the Technical Guide (2015).

Methylcellulose (0345)

This text corresponds to Revision 3, Stage 5B within the Pharmacopoeial harmonisation process (Ph. Eur., JP, USP).

Assay: chromatographic conditions modified to replace the packed column by a capillary column.

Nystatin (0517)

Production: section deleted as the test for abnormal toxicity (*2.6.9*) was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Pantoprazole sodium sesquihydrate (2296)

Related substances: reference solution (b) updated following change of the production mode in the CRS used for system suitability and reagent used to describe stationary phase modified.

Pentobarbital (0200)

Definition: lower and upper content limits modified to reflect change in assay method.

Solubility: grade of ethanol specified.

Identification B: chloroform replaced by methylene chloride.

Related substances: TLC replaced by LC capable of controlling 6 unspecified impurities.

Isomer: test deleted as impurity E now controlled by related substances test.

Assay: titration using pyridine and end-point determination by colour indicator replaced by LC method used in related substances test.

Impurities: section introduced.

Pentobarbital sodium (0419)

Definition: lower and upper content limits modified to reflect change in assay method.

Identification B: preparation of test solution modified and chloroform replaced by methylene chloride.

Related substances: TLC replaced by LC capable of controlling 6 unspecified impurities.

Isomer: test deleted as impurity E now controlled by related substances test.

Assay: titration using pyridine and end-point determination by colour indicator replaced by LC method used in related substances test.

Impurities: section introduced.

Peritoneal dialysis, solutions for (0862)

Aluminium: qualitative test method replaced with atomic absorption spectrometry (AAS) (quantitative test).

Total chloride: assay method using dibutyl phthalate reagent (included in Annex XIV of REACH regulation) replaced with potentiometric titration.

Phenytoin (1253)

Content: lower and upper limits updated to reflect change in assay method.

Related substances: reagent used to describe stationary phase modified.

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

Phenytoin sodium (0521)

Content: lower and upper limits updated to reflect change in assay method.

Characters: degree of hygroscopicity updated.

Related substances: reagent used to describe stationary phase modified.

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

Potassium sulfate (1622)

Identifications A and B: reaction (a) is sufficient.

Assay: new method described avoiding the use of lead nitrate.

Primaquine diphosphate (0635)

Related substances: method replaced by improved LC method; specifications updated.

Impurities: section added.

Protamine sulfate (0569)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Rifamycin sodium (0432)

Production: test for abnormal toxicity (*2.6.9*) deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Related substances: reagent used to describe stationary phase modified.

Ropinirole hydrochloride (2604)

Related substances: impurity E now listed as a specified impurity and limit increased to 0.15 per cent based on new batch data; grades of solvents amended in accordance with the Technical Guide (2015).

Sodium sulfate, anhydrous (0099)

Identifications A and B: reaction (a) is sufficient.

Assay: new method described avoiding the use of lead nitrate.

Sodium sulfate decahydrate (0100)

Identifications A and B: reaction (a) is sufficient.

Assay: new method described avoiding the use of lead nitrate.

Starches, hydroxyethyl (1785)

Molecular weight (Mw) and molecular weight distribution: grade of solvent amended in accordance with Technical Guide (2015).

Molar substitution (MS): elution order replaced by information on relative retention of iodoethane.

Ethylene glycol: grade of solvent amended in accordance with Technical Guide (2015); reagents used to describe stationary phases modified.

2-Chloroethanol: reference solution must be prepared with solvent mixture, as for test solution.

Streptokinase concentrated solution (0356)

Production: section deleted as the test for abnormal toxicity (*2.6.9*) was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Related substances: mobile phase A corrected.

Streptomycin sulfate (0053)

Production: test for abnormal toxicity (*2.6.9)* deleted; the test was considered to be outdated and shown to be neither specific, reproducible, reliable nor suitable for the intended purpose and its removal would not compromise safety.

Tigecycline (2825)

Assay: only impurity A required for the system suitability, so new reference solution (d) described under Related substances.