Comments concerning revised texts published in Supplement 8.3

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November 2013 session and published in Supplement 8.3.

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

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

GENERAL CHAPTERS

2.2.29. Liquid chromatography

The chapter has been revised to include a reference to LC systems using short columns and reduced particle-size stationary phases, such as sub-2 µm particles, and mobile phases at high pressure but avoiding reference to trading names such as e.g. UPLC, RRLC, etc.

2.4.22. Composition of fatty acids by gas chromatography

Content of oleic acid: sentence added to clarify that content of oleic acid is sum of oleic acid (18:1 n-9) and cis-vaccinic acid (18:1 n-7).

2.7.5. Assay of heparin

The clotting assay in sheep plasma has been replaced by a more specific chromogenic assay for anti-factor IIa activity following an international collaborative study (Gray E., Hogwood J., Rigsby P. et al. An international collaborative study to value assign the 6th international standard for unfractionated heparin and the US pharmacopeial heparin reference standard for assay lot F. Ref: WHO/BS/09.2124. WHO Expert Committee on Biological Standardization; 2009).

The revised chapter also comprises an assay for anti-factor Xa activity, which is used to establish the ratio of anti-factor Xa to anti-factor IIa activity, used as an identification criterion in the unfractionated heparin monographs (heparin sodium (0333), heparin calcium (0332)). As part of this revision, heparin sodium BRP was recalibrated for use with these new methods.
3.2.1. Glass containers for pharmaceutical use

**Production**: section introduced to address the risk related to potential delamination of glass containers, by raising awareness of the glass manufacturers and users of the glass containers in the pharmaceutical industry to the factors contributing to the phenomenon.

**Harmonisation with ISO 4802-1 and 4802-2**: adjustments made to avoid ambiguities with ISO, including an additional volume specification for containers of 2-3 mL in Table 3.2.1.-3 and Table 3.2.1.-7.

**Hydrolytic resistance of glass grains**: alternative grinding device introduced to include state-of-the-art equipment that increases reproducibility of sample preparation.

5.8. Pharmacopoeial harmonisation

Degree of harmonisation included for 8 additional monographs and information on Ph. Eur. provisions for general chapter 5.1.4. modified.

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**VACCINES FOR HUMAN USE**

**Diphtheria and tetanus vaccine (adsorbed, reduced antigen(s) content) (0647)**

*Definition*: sentence concerning adverse reactions deleted (safety requirement usually not part of a definition) and information on reduced antigen content added, in order to align with *Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content)* (2764).

**Diphtheria vaccine (adsorbed, reduced antigen content) (0646)**

*Definition*: sentence concerning adverse reactions deleted (safety requirement usually not part of a definition) and information on reduced antigen content added, in order to align with *Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content)* (2764).

**Haemophilus type b conjugate vaccine (1219)**

*Carrier protein*: section replaced by reference to requirements now described in new general chapter 5.2.11. *Carrier proteins for the production of conjugated polysaccharide vaccines for human use*, also published in Supplement 8.3.

*Tables 1219.-1 and 1219.-2*: deleted.

*Bulk conjugate-PRP*: anion-exchange LC with pulsed amperometric detection added, as method already mentioned under Final lot.

**Meningococcal group C conjugate vaccine (2112)**

*Carrier protein*: section replaced by reference to requirements now described in new general chapter 5.2.11. *Carrier proteins for the production of conjugated polysaccharide vaccines for human use*, also published in Supplement 8.3.

*pH*: specification replaced by ‘within the limits approved for the particular product’.
Pneumococcal polysaccharide conjugate vaccine (adsorbed) (2150)

Carrier protein: section replaced by reference to requirements now described in new general chapter 5.2.11. Carrier proteins for the production of conjugated polysaccharide vaccines for human use, also published in Supplement 8.3.

VACCINES FOR VETERINARY USE

Foot-and-mouth disease (ruminants) vaccine (inactivated) (0063)

Safety (section 2-4-1). Section harmonised with VICH Guideline 44 (8 animals instead of 10; double dose vaccination replaced by a single dose vaccination; observation period of at least 14 days).

Safety in pregnant animals (formerly section 2-4-1-2). The protocol and acceptance limits of this test are fully described in general chapter 5.2.6. This test is included in a specific monograph only when there is a particular risk associated with vaccination during pregnancy or when the vaccine is specifically indicated for use in pregnant animals. Since this is not the case for this vaccine, the test has been deleted. Since this test is required for all veterinary vaccines by the general monograph on Vaccines for veterinary use (0062) and described in general chapter 5.2.6., this is not a lowering of requirements, but a standardisation in order to avoid duplication; indeed, this test has still to be carried out if the vaccine is indicated for use or may be used in pregnant animals.

Immunogenicity (section 2-4-2). The monograph has been revised to describe 2 tests appropriate to demonstrate immunogenicity of foot-and-mouth disease vaccines intended for cattle: the previous PD$_{50}$ challenge test and in addition, the ‘percentage of protection against generalised foot infection’ (PPG test), which is also described in the World Organisation for Animal Health (OIE) Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2012 (chapter 2.1.5. Foot-and-mouth disease). Challenge after 20-22 days instead of 21 days (3 weeks) to harmonise with other similar monographs.

Batch potency test (section 2-5-4). The requirement ‘titres at least equal to the pass level are measured in not fewer than 50 per cent of the cattle’ was changed to ‘if the geometric mean of the antibody titre in cattle is not significantly lower than the pass level’ to be in line with other monographs.

Target-animal batch safety test (formerly section 3-3). Test deleted.

The term ‘serotypes’ has been replaced by the term ‘strains’ throughout the text.

Furthermore, ‘minimum/maximum potency’ was replaced by ‘minimum/maximum antigen content’ where appropriate.

Furunculosis vaccine (inactivated, oil-adjuvanted, injectable) for salmonids (1521)

This revision is based on recently published work: Romstad AB et al. Development of an antibody ELISA for potency testing of furunculosis (Aeromonas salmonicida subsp salmonicida) vaccines in Atlantic salmon (Salmo salar L). Biologicals 2012; 40(1):67-71.
**Immunogenicity**: test based on end-point mortality rather than 60 per cent control mortality; RPS requirement lowered to 70.

**Batch potency test**: important factors specified: temperature not less than 12 °C, collection time not less than 500 degree days after vaccination.

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**HERBAL DRUGS AND HERBAL DRUG PREPARATIONS**

**Agnus castus fruit (2147)**

*Total ash*: limit widened in accordance with literature.

*Assay*: LC method amended to avoid high pressure. Reference substance renamed ‘agnus castus fruit dry extract HRS’.

**Aloes, Barbados (0257)**

*Identification*: section revised to avoid use of disodium tetraborate (REACH); tests B and C deleted and TLC replaced by improved TLC/HPTLC method.

*Cape aloe*: test introduced.

**Aloes dry extract, standardised (0259)**

*Identification*: section revised to avoid use of disodium tetraborate (REACH); test B deleted and TLC replaced by improved TLC/HPTLC method.

**Fraxinus rhynchophylla bark (2452)**

*Assay*: change of the solvent used for the reference solutions to avoid artefacts observed with the previous solvent.

**Opium dry extract, standardised (1839)**

Monograph harmonised with *Standardised opium tincture (1841)*, *Raw opium (0777)* and *Prepared opium (1840)*.

**Opium, prepared (1840)**

*Identification*: microscopic identification updated; conditions for HPTLC added.

*Tests/Assay*: reagents used as reference substances replaced by CRS; description of reference solutions and calculation formula adapted accordingly.

**Opium, raw (0777)**

*Identification*: microscopic identification updated; conditions for HPTLC added.

*Tests/Assay*: reagents used as reference substances replaced by CRS; description of reference solutions and calculation formula adapted accordingly.
Opium tincture, standardised (1841)
   Monograph harmonised with Standardised opium dry extract (1839), Raw opium (0777) and Prepared opium (1840).

Pygeum africanum bark (1886)
   Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Rhatany root (0289)
   Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Rhatany tincture (1888)
   Identification: sample preparation deleted as unnecessary; HPTLC conditions added.

Sage leaf (Salvia officinalis) (1370)
   Definition: in accordance with recent batch data, essential oil content for whole drug lowered to minimum 12 mL/kg.
   Characters: section deleted.
   Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Senna leaf (0206)
   Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of identification B.
   Assay: in accordance with practical observations, the volume of hydrochloric acid used to dissolve the precipitate has been modified.

Senna pods, Alexandrian (0207)
   Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of identification B.
   Assay: in accordance with practical observations, the volume of hydrochloric acid used to dissolve the precipitate has been modified.

Senna pods, Tinnevelly (0208)
   Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of identification B.
   Assay: in accordance with practical observations, the volume of hydrochloric acid used to dissolve the precipitate has been modified.
Sophora flower (2639)

*Rutin*: preparation of reference solution (b) changed due to solubility problems.

Sophora flower-bud (2427)

*Rutin*: preparation of reference solution (b) changed due to solubility problems.

Turmeric, Javanese (1441)

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

*Identification C*: TLC method for distinction between *Curcuma zanthorrhiza* and *C. longa* improved and HPTLC conditions added.

*Assay of essential oil*: amount of sample reduced to avoid obtaining volumes of essential oil greater than the volume of the graduated tube and to reduce foaming during distillation.

*Assay of dicinnamoyl methane derivatives*: method revised to avoid using boric acid (REACH) and harmonised with the method in the monograph *Turmeric rhizome* (2543).

Turmeric rhizome (2543)

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

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### HOMOEOPATHIC PREPARATIONS

Homoeopathic preparations (1038)

*Potentisation*: brief description for LM potencies added.

*Dosage forms*: principles from HAB (German Homoeopathic Pharmacopoeia) method 16 (mixtures) added; section for homoeopathic dosage form ‘pillule’ harmonised with monographs *Pillules for homoeopathic preparations* (2153) and *Impregnated homoeopathic pillules* (2079); homoeopathic dosage forms ‘parenteral preparation’, ‘eye preparation’ and ‘nasal preparation’ added. Uniformity requirement deleted as given in general monograph *Pharmaceutical preparations* (2619).

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### MONOGRAPHS

Acetic acid, glacial (0590)

*Reducing substances*: test revised to replace potassium dichromate (proscribed under REACH regulation).
Almond oil, virgin (0261)

Absorbance: instruction introduced to ensure absorbance within linear range.

D-Camphor (1400)

Specific optical rotation: limits revised based on batch data.

Castor oil, refined (2367)

Composition of fatty acids: term 'and isomers' deleted from limit for oleic acid since separation of oleic acid and its isomers (mainly cis-vaccinic acid) may not be achieved with current method.

Clarification that content of oleic acid is sum of oleic acid (18:1 n-9) and cis-vaccinic acid (18:1 n-7) has been included in general method 2.4.22. Composition of fatty acids by gas chromatography.

Castor oil, virgin (0051)

Composition of fatty acids: term 'and isomers' deleted from limit for oleic acid since separation of oleic acid and its isomers (mainly cis-vaccinic acid) may not be achieved with current method.

Clarification that content of oleic acid is sum of oleic acid (18:1 n-9) and cis-vaccinic acid (18:1 n-7) has been included in general method 2.4.22. Composition of fatty acids by gas chromatography.

Chlorhexidine diacetate (0657)

Choroaniline: test replaced by absorption spectrophotometry.

Related substances: LC method replaced with that described in monograph Chlorhexidine digluconate solution (0658); based on batch and stability results, limits for individual impurities added.

Chlorprothixene hydrochloride (0815)

Identification A: quantity of sample reduced.

Related substances: impurity F now quantified against dilution of test solution.

Clindamycin phosphate (0996)

Definition: content limits revised to reflect current market quality.

pH, Specific optical rotation: tests removed.

Related substances, Assay: improved LC introduced to allow identification of additional impurities; limits revised to reflect current market quality.

Water: sample size reduced and limit lowered to reflect current market quality.

Impurities: section updated.
Coconut oil, refined (1410)

*Composition of fatty acids*: term ‘and isomers’ deleted from limit for oleic acid since separation of oleic acid and its isomers (mainly cis-vaccinic acid) may not be achieved with current method.

Clarification that content of oleic acid is sum of oleic acid (18:1 n-9) and cis-vaccinic acid (18:1 n-7) has been included in general method 2.4.22. *Composition of fatty acids by gas chromatography.*

Diosmin (1611)

*Related substances*: substance is obtained through iodine oxidation of hesperidin (natural origin). Therefore, the thresholds indicated in the general monograph *Substances for pharmaceutical use* (2034) do not apply, corresponding statement introduced. Limits updated based on recent batch data; additional impurity introduced; system suitability CRS used for identification of the specified impurities; impurities A-F now listed as specified impurities.

Ethanol (96 per cent) (1317)

*Volatile impurities*: formula for calculation of the content of acetaldehyde and acetal has been corrected.

Ethanol, anhydrous (1318)

*Volatile impurities*: formula for calculation of the content of acetaldehyde and acetal has been corrected.

Ethionamide (0141)

*Definition*: upper limit for content increased to 101.5 per cent in order to have symmetrical limits.

*Identification*: 1st identification limited to test C as IR considered sufficient.

*Appearance of solution*: test deleted as no parenteral administration known.

*Related substances*: TLC replaced by LC; limits updated according to current quality of products on the European market: limit for specified impurity A set to 0.2 per cent, limit for unspecified impurities now in line with general monograph *Substances for pharmaceutical use* (2034); reporting threshold and limit for total of impurities introduced.

*Impurities*: section added.

Etoposide (0823)

*Content*: upper limit raised.

Fibrin sealant kit (0903)

*Assay (component 2)*: currently licensed fibrin sealant kit products contain 2 concentrations (high and low) of component 2 (thrombin preparation), giving clinicians control over the use of slow or fast fibrin generation. The monograph has been revised to bring it into agreement with all licensed products on the market.
Follitropin (2285)

The monograph has been revised further to the establishment of 2 follitropin reference standards: *follitropin for peptide mapping and glycan analysis CRS*, for use in these 2 tests, and *follitropin CRS* for use in the other tests except the potency assay.

**Identification D**: for the separation of the α and β-subunits, the characteristics of the precolumn now correspond to the column given as an example.

**Identification E, method A**: the volume of particle-free water R added before labelling has been corrected (English version only).

**Identification E, method B**: the settings of the pulsed amperometric detector are now specified.

**Follitropin oligomers**: the concentration of *bovine albumin R* in solution B has been increased; the resolution requirement for system suitability has been lowered.

**Free subunits**: the system suitability requirement for recovery has been deleted.

Changes to the COM document adopted at the 147th session relate to the preparation of all reference solutions prepared with *follitropin CRS* and *follitropin for peptide mapping and glycan analysis CRS*, which are presented as solutions and not powders.

Follitropin concentrated solution (2286)

The monograph has been revised further to the establishment of 2 follitropin reference standards: *follitropin for peptide mapping and glycan analysis CRS*, for use in these 2 tests, and *follitropin CRS* for use in the other tests except the potency assay.

**Identification D**: for the separation of the α and β-subunits, the characteristics of the precolumn now correspond to the column given as an example.

**Identification E, method B**: the settings of the pulsed amperometric detector are now specified.

**Follitropin oligomers**: the concentration of *bovine albumin R* in solution B has been increased; the resolution requirement for system suitability has been lowered.

**Free subunits**: the system suitability requirement for recovery has been deleted.

Changes to the COM document adopted at the 147th session relate to the preparation of all reference solutions prepared with *follitropin CRS* and *follitropin for peptide mapping and glycan analysis CRS*, which are presented as solutions and not powders.

Furosemide (0391)

**Appearance of solution**: since the substance is used in parenteral preparations, the test has been introduced in accordance with the Technical guide.

**Related substances**: an additional system suitability criterion has been added in accordance with the requirements in the Technical guide.

**Assay**: volume of solvent increased.

Gelatin (0330)

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

**Gemcitabine hydrochloride (2306)**

*Related substances:* β-uridine (impurity C) added as a specified impurity; limits for impurity A and for the total have been updated.

**Heparin calcium (0332)**

*Definition.* The scope has been restricted to heparin material of porcine origin since some of the latest requirements do not apply to materials of other origins and that heparin medicinal products currently on the European market are all of porcine origin. Further to the replacement of the clotting assay by 2 chromogenic assays for anti-factor IIa activity and anti-factor Xa activity in general chapter 2.7.5. *Assay of heparin,* potency is now measured by the assay of anti-factor IIa activity.

*Production.* A statement was introduced during the last revision, which requires testing for identity of the source species and the absence of material from other likely cross-contaminant species. Further indications have been added that reflect current widely spread practices.

*Identification:* a requirement for the ratio of anti-factor Xa activity to anti-factor IIa activity has been introduced; a ratio of 1 is typical of unfractionated heparin.

**Heparin sodium (0333)**

*Definition.* The scope has been restricted to heparin material of porcine origin since some of the latest requirements do not apply to materials of other origins and that heparin medicinal products currently on the European market are all of porcine origin. Further to the replacement of the clotting assay by 2 chromogenic assays for anti-factor IIa activity and anti-factor Xa activity in general chapter 2.7.5. *Assay of heparin,* potency is now measured by the assay of anti-factor IIa activity.

*Production.* A statement was introduced during the last revision, which requires testing for identity of the source species and the absence of material from other likely cross-contaminant species. Further indications have been added that reflect current widely spread practices.

*Identification:* a requirement for the ratio of anti-factor Xa activity to anti-factor IIa activity has been introduced; a ratio of 1 is typical of unfractionated heparin.

*Sodium:* range modified in line with current batch data.

**Human anti-D immunoglobulin (0557)**

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration).

**Human coagulation factor VIIa ( rDNA) concentrated solution (2534)**

*Glycan analysis:* the test has been moved to the Production section of the monograph, according to the provisions given in the General Notices, as the test cannot be performed by an independent analyst for the following reasons: the user needs acceptance criteria in the form of numerical limits, which are not prescribed in the monograph; the respective specifications have to be set in agreement with the competent authority.
**Gla-domainless human coagulation factor VIIa (rDNA) (gamma-carboxylation):** a statement on peak integration has been added.

**Dimers and related substances of higher molecular mass:** the symmetry factor has been corrected and an additional system suitability criterion has been introduced.

**Human hepatitis A immunoglobulin (0769)**

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration).

**Human hepatitis B immunoglobulin (0722)**

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration). Additionally, the monograph has been updated to include *Human hepatitis B immunoglobulin BRP*.

**Human hepatitis B immunoglobulin for intravenous administration (1016)**

The monograph has been updated to include *Human hepatitis B immunoglobulin BRP*.

**Human measles immunoglobulin (0397)**

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration).

**Human normal immunoglobulin for intramuscular administration (0338)**

*Intramuscular administration.* Title of monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration). Monograph revised to recognise specific requirements of human normal immunoglobulin for intramuscular administration and reflect the products currently on the market.

**Human plasma (pooled and treated for virus inactivation) (1646)**

*Hepatitis E virus RNA.* A test for hepatitis E virus (HEV) RNA by NAT has been introduced further to the identification that 10 per cent of plasma pools available in the world are positive for HEV RNA (S.A. Baylis et al. Widespread distribution of hepatitis E virus in plasma fractionation pools. Vox Sang. 2012; 102(2):182-3). Based on the knowledge of the prevalence of HEV RNA in plasma pools, the test acts as a risk minimisation for potential HEV transmission.

**Human rabies immunoglobulin (0723)**

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration).
Human rubella immunoglobulin (0617)

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration).

Human tetanus immunoglobulin (0398)

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration).

Human varicella immunoglobulin (0724)

Monograph updated to reflect separation of intramuscular and subcutaneous administration routes for human normal immunoglobulin into 2 separate monographs (intramuscular (0338) and subcutaneous (2788) administration).

Hydroxypropylcellulose (0337)

The following changes are the result of pharmacopoeial harmonisation.

**Definition/assay**: assay based on Zeissel reaction (determination of alkoxy groups in substituted cellulose) added; addition of anticaking agents permitted.

**Characters**: section simplified.

**Identification**: most wet chemistry tests replaced by IR.

**Appearance of solution**: test deleted as excipient not used in parenteral preparations.

**Loss on drying, Sulfated ash**: limits reduced to reflect quality on market.

**Functionality-related characteristics**: section added.

This monograph has in addition 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.

Isomalt (1531)

The following changes are the result of pharmacopoeial harmonisation:

**Conductivity**: guidance regarding solution preparation included.

**Related substances**: tolerance for column temperature increased; run time expressed with reference to retention time of one component of isomalt (1,1-GPM); system suitability test added.

**Lead**: test deleted because there is no particular reason to test for this metal specifically.

**Nickel**: method revised to increase sensitivity.

**Impurities**: requirements of Table 2034.-1 in Substances for pharmaceutical use (2034) do not apply since isomalt is an excipient.

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

**Lactulose (1230)**

*Identification A*: TLC silica gel G plate R replaced by TLC silica gel plate R.

*Related substances*: limits for specified, unspecified and total impurities, and disregard limit included; system suitability requirement modified in accordance with recent revision of monograph *Lactulose, liquid (0924).*

*Impurities*: list of specified and unspecified impurities added.

**Magnesium hydroxide (0039)**

*Sulfates*: limit increased based on batch data.

**Magnesium stearate (0229)**

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

**Meldonium dihydrate (2624)**

*Related substances*: due to low absorption in the UV-range, specified impurities are detected by multiple reaction monitoring (MRM); in the absence of any other suitable detection option, the total ion current (TIC) is used for unspecified impurities.

**Methotrexate (0560)**

*Enantiomeric purity*: (RS)-methotrexate R replaced by methotrexate for system suitability CRS as it is no longer available on the market.

**Methylene chloride (0932)**

*Ethanol, 2-methylbut-2-ene and volatile impurities*: quantitative expression of acceptance criteria introduced.

**Neostigmine bromide (0046)**

*Related substances*: reference solutions revised.

**Neostigmine metilsulfate (0626)**

*Related substances*: reference solutions revised.

**Nicotine resinate (1792)**

*Characters*: hygroscopicity added.

*Water*: test replaced by loss on drying, limit increased.
Phytomenadione (1036)

Assay: formulas deleted, if needed information on how to perform the calculation of content will be supplied in the leaflet of phytomenadione CRS.

Piperacillin (1169)

Specific optical rotation: limits adjusted to reflect current quality of product on the market.

Prilocaine (1362)

Related substances: new peak identification CRS introduced for identification of new specified impurity G.

Impurities: impurity G added.

Prilocaine hydrochloride (1363)

Identification C: TLC plate replaced.

Related substances: new peak identification CRS introduced for identification of new specified impurity G.

Impurities: impurity G added.

Probenecid (0243)

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

Heavy metals: method C replaced by method H according to current policy. Given the maximum daily dose of > 0.5 g/day and duration of treatment > 30 days, limit has been decreased.

Impurities: impurities controlled by LC added.

Progesterone (0429)

Content: upper limit updated to reflect changes in assay method.

Identification: detection B deleted from TLC.

Related substances: LC method adapted to allow separation of additional specified impurities; limits revised based on information available.

Assay: UV replaced by same LC method used for related substances.

Impurities: updated based on available data.

Saccharin (0947)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8, Pharmacopoeial harmonisation.
Silica, colloidal hydrated (0738)

**Definition:** production process indicated to differentiate from anhydrous silica.

**Identification:** loss on drying deleted as not appropriate for identification purposes.

Sodium alendronate trihydrate (1564)

**Title:** degree of hydration added.

**Identification:** cross-reference to test for loss on drying added to distinguish from other hydrate forms.

**Appearance of solution:** test deleted as substance is only for oral use.

**Related substances:** TLC for 4-aminobutanoic acid replaced by LC.

Sodium aminosalicylate dihydrate (1993)

**Identification A:** replacement of the IR reference spectrum by a CRS in accordance with current policy.

**Pyrogens:** The European Pharmacopoeia Commission has a policy of regular review of animal tests prescribed in monographs with a view to their replacement by *in vitro* methods wherever possible, in accordance with the EU Directive 2010/63/EU. Therefore, the test for pyrogens has been deleted.

Sodium starch glycolate (type A) (0983)

The following changes are the result of pharmacopoeial harmonisation:

**Definition:** all sources of starch may be used.

**Characters:** microscopic examination deleted.

**Sodium chloride:** further information regarding electrode included.

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

Sodium starch glycolate (type B) (0984)

The following changes are the result of pharmacopoeial harmonisation:

**Definition:** all sources of starch may be used.

**Characters:** microscopic examination deleted.

**Sodium chloride:** further information regarding electrode included.

This monograph has in addition been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8, *Pharmacopoeial harmonisation*. 
**Sodium starch glycolate (type C) (1566)**

*Sodium chloride*: additional information regarding electrode included.

In contrast to the monographs Sodium starch glycolate type A and type B (0983 and 0984), this monograph has not undergone pharmacopoeial harmonisation.

**Stavudine (2130)**

*Related substances*: impurity G included as a specified impurity with a limit of 0.2 per cent, quantitative expression of acceptance criteria applied.

*Impurity I*: specific LC method introduced to control this new specified impurity.

*Assay*: relative retentions of impurities added.

**Sucrose (0204)**

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*.

**Tryptophan (1272)**

*Definition*: scope of monograph added.

*Ninhydrin-positive substances*: TLC replaced by LC using amino acid analysis; same method used to quantify ammonium.

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

**Xylazine hydrochloride for veterinary use (1481)**

*Characters*: polymorphism statement introduced for information.

*Identification A*: if polymorphs exhibit different spectra, the recrystallisation procedure can be used.

**Xylitol (1381)**

*Identification C*: test improved, now using TLC plates with organic binder. CRSs for system suitability purposes replaced by reagents.

**Ziprasidone hydrochloride monohydrate (2421)**

*Related substances*: preparation of reference solution (a) amended to prevent degradation; pH of mobile phase slightly modified to improve separation.