

Comments concerning revised texts published in Supplement 9.7

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the March 2018 session and published in Supplement 9.7.

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

2.2.24. Absorption spectrophotometry, infrared

The general chapter has been completely rewritten and its structure updated. This general revision includes: an extended description of ATR FT-IR instruments and related criteria for control of equipment performance; the removal of monochromator instruments as they are no longer in use; a new section on principle, with distinction between near-, mid- and far-infrared; new sections on applications and limitations; a reduction from 7 to 4 band positions used for verification of the wavenumber scale following removal of monochromator instruments, and addition of slightly shifted band positions for ATR FT-IR instruments; guidance on the use of stored spectra and internal libraries; a description of procedures for the comparison of spectra.

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

EPA and DHA: the description of the reagent *boron trichloride-methanol solution R* has been corrected; the stationary phase has been modified; a clarification has been added regarding the use of test solution (b), as it is not always possible to satisfy simultaneously the requirements for symmetry factor and clear detection of all peaks.

2.7.14. Assay of hepatitis A vaccine

Method A: following suppression of the Ph. Eur. monograph *Water, highly purified (1927)* as of Supplement 9.7, *highly purified water R* has been replaced with *water for injections R*.

2.9.23. Gas pycnometric density of solids

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

2.9.31. Particle size analysis by laser light diffraction

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

Instrument: Figure 2.9.31.-1 has been corrected.

2.9.33. Characterisation of crystalline and partially crystalline solids by X-ray powder diffraction (XRPD)

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

2.9.34. Bulk density and tapped density of powders

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

2.9.35. Powder fineness

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

2.9.39. Water-solid interactions: determination of sorption-desorption isotherms and of water activity

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

5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use

Text revised to specify that it does not cover medicinal products containing viable micro-organisms (live biotherapeutic products). These products are covered by the new general monograph *Live biotherapeutic products for human use (3053)*, which is published in the same supplement.

This modification is applied in the Ph. Eur. as a local requirement.

5.1.8. Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation

Text revised to indicate that medicinal products containing live yeasts (live biotherapeutic products) are not within the scope of this general chapter. Microbiological examination of live biotherapeutic products is performed according to the methods described in the new general

chapters 2.6.36 and 2.6.38 and the acceptance criteria are specified in the new general monograph *Live biotherapeutic products for human use (3053)*, which are published in the same supplement.

5.8. Pharmacopoeial harmonisation

Information added for 6 general chapters and deleted for 3 monographs (bilateral harmonisation only).

5.14. Gene transfer medicinal products for human use

Production - Substances used in production: following suppression of the Ph. Eur. monograph *Water, highly purified (1927)* as of Supplement 9.7 (which is now fully covered by the revised monograph for *Water for injections (0169)*), the reference to this monograph has been deleted.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include new monographs published in Supplement 9.7.

5.23. Monographs on herbal drug extracts (information chapter)

Differentiation between DER_{genuine} and DER_{total} improved.

GENERAL MONOGRAPHS

Herbal drug extracts (0765)

Definition of drug extract ratio (DER) amended to improve differentiation between DER_{genuine} and DER_{total} .

Pharmaceutical preparations (2619)

Definition: a reference to the new general monograph *Live biotherapeutic products for human use (3053)*, published in the same supplement, has been added.

Production: all references to the general texts that apply when biological materials of animal or human origin are used, some of which were initially found in the Definition section, have been grouped together under Production, in compliance with the respective objectives of these 2 sections as defined in the General Notices.

Recombinant DNA technology, products of (0784)

The monograph has undergone a general revision to take into account current practices and advances in the field of recombinant DNA technology.

Scope: the scope has been clarified and extended to include modified proteins, proteins obtained in transgenic animals and plants, and recombinant vaccine antigens.

Production: the section has been entirely re-structured and modernised in line with the requirements of ICH, EMA and WHO guidelines for recombinant proteins. A subsection on the characterisation of the active substance has been introduced, and outlines the elucidation of

recombinant protein properties including structure determination, content, biological activity, purity profile, analysis of any post-translational modifications (e.g. glycosylation) and of any other intentional modification. Likewise, a subsection briefly describing the establishment of a control strategy and how release specifications fit into the overall strategy is also introduced.

Identification, Tests, Assay: general considerations regarding the identification and assay of recombinant products, and for testing at the active substance and finished product stages, have been introduced.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Atractylodes lancea rhizome (2559)

Identification: more detailed description provided for Identification A; illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Atractylodes rhizome, largehead (2560)

Identification: more detailed description given for Identification A; illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

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

Production: a concentration range, instead of a single value, is specified for ethanol used as production solvent.

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

Kudzuvine root (2434)

Definition: section updated.

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

Peppermint oil (0405)

Definition: modified for greater clarity.

Mint oil: test A by TLC deleted and now used only for Identification A.

Saw palmetto fruit (1848)

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

Thomson kudzuvine root (2483)

Definition: section updated.

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

MONOGRAPHS

Acetone (0872)

Water: pyridine replaced as solvent.

Alfentanil hydrochloride hydrate (1062)

Title, Definition: modified to reflect that the monograph covers different hydrate forms in accordance with policy described in the Technical Guide (2015).

Characters: statement on polymorphism added.

Identification A: reference spectrum replaced by reference substance; recrystallisation step introduced.

Related substances: specifications updated in order to reflect the quality of substances in approved medicinal products on the European market; explicit criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; grades of solvents amended in accordance with the Technical Guide (2015).

Amfetamine sulfate (0368)

Content: upper limit modified in accordance with the Technical Guide recommendations for potentiometric titration assays.

Characters: solubility in ethanol (96 per cent) updated and solubility in methylene chloride introduced.

Identification: optical rotation now described under Tests; sample preparation for IR deleted and CRS introduced; former identification test D (colour reaction) deleted.

Related substances: LC test introduced, covering 4 new unspecified impurities.

Impurities: section added.

Amiloride hydrochloride dihydrate (0651)

Identification: test B TLC method modified to avoid use of dioxan; previous test C deleted; test for chlorides revised.

Amorolfine hydrochloride (2756)

Identification B: method updated.

Related substances: volume of reference solution (a) modified to lower the accuracy requirement; reagent used to describe stationary phase modified and grade of solvents amended in accordance with the Technical Guide (2015); additional impurities controlled by the current method.

Impurities: section updated.

Betacarotene (1069)

Definition: updated to clarify that all-*trans*-betacarotene is the main component; lower and upper content limits revised.

Solubility: section updated.

Identification A: chloroform replaced with tetrahydrofuran.

Related substances: UV test replaced by LC.

Sulfated ash: limit and procedure aligned with JEFCA (Joint FAO/WHO Expert Committee on Food Additives) monograph.

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

Storage: indication of temperature deleted.

Impurities: section introduced.

Calcium folinate hydrate (0978)

Title: revised as substance an undefined hydrate.

CAS number: modified.

Characters: substance shows polymorphism.

Acetone, ethanol and methanol: test revised to cover ethanol only, and renamed accordingly.

Related substances: test revised to improve separation of impurities and cover an additional impurity.

Platinum: test deleted in line with Ph. Eur. implementation strategy for ICH Q3D guideline on elemental impurities.

Water: lower limit specified.

Bacterial endotoxins: test removed in accordance with current policy.

Impurities: section updated.

Calcium levofolate hydrate (1606)

Title, CAS number: title revised and CAS number deleted as substance not a defined hydrate.

Characters: substance shows polymorphism.

Acetone and ethanol: test revised to cover ethanol only, and renamed accordingly.

Related substances: test revised to improve separation of impurities and cover an additional impurity.

Impurity H: reagent used to describe stationary phase modified.

Platinum: test deleted in line with Ph. Eur. implementation strategy for ICH Q3D guideline on elemental impurities.

Water: same method used as for *Calcium folinate hydrate (0978)*.

Bacterial endotoxins: test removed in accordance with current policy.

Impurities: section updated.

Castor oil, refined (2367)

Appearance (colour): reference solution replaced by reference solutions described in chapter 2.2.2 and specification less stringent.

Storage: section updated.

Labelling: section updated.

Cefazolin sodium (0988)

Related substances: reagent used to describe stationary phase modified, and grade of solvent amended in accordance with the Technical Guide (2015).

Assay: reagent used to describe stationary phase modified, and system suitability requirements revised.

Cellulose acetate (0887)

Further to decisions taken at the September 2017 PDG meeting, this monograph has been withdrawn from the PDG work programme and consequently from chapter 5.8. It remains the ultimate responsibility of the user to verify the current content of the texts in force in the respective pharmacopoeias.

Chloramphenicol (0071)

Second identification: description of melting point modified slightly.

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

Closantel sodium dihydrate for veterinary use (1716)

Degree of hydration: wording introduced to specify that CAS number of anhydrous substance is listed and relative molecular mass of anhydrous substance now given in accordance with the policy on hydrates described in the Technical Guide (2015).

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

Dipotassium clorazepate monohydrate (0898)

Title: degree of hydration indicated.

Characters: statement on hygroscopicity added.

Identification B: IR sample preparation deleted.

Related substances: TLC replaced by LC which is able to control an additional specified impurity.

Impurity B: LC test introduced.

Loss on drying: test replaced by volumetric Karl Fischer determination of water.

Impurities: section updated.

Dosulepin hydrochloride (1314)

Related substances: accuracy of volume of reference solution (b) decreased; reagent used to describe stationary phase modified; retention time of dosulepin and relative retention of impurity E updated.

Entecavir monohydrate (2815)

Specific optical rotation, Water: limits widened.

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

Ergocalciferol (0082)

Related substances, Assay: description of new method allowing baseline separation of peaks due to impurity A, pre-ergocalciferol and ergocalciferol introduced; limits updated.

Ethylcellulose (0822)

Functionality-related characteristics (FRCs): section updated with FRCs for the substance used as matrix former in modified release oral dosage forms: viscosity, degree of substitution, particle-size distribution and powder flow.

Fibrin sealant kit (0903)

Component 1 (fibrinogen concentrate)

Production: clarification added regarding the requirement to carry out an assay of human coagulation factor XIII when the label states that it is an active substance in component 1; sentence added to reflect the situation of products for which human coagulation factor XIII is not declared as an active substance in component 1.

Assay (Human coagulation factor XIII): text amended to better reflect the situation of products for which factor XIII potency specifications are provided as a range.

Glipizide (0906)

Related substances: grade of solvents in solvent mixture and mobile phase B amended in accordance with the Technical Guide (2015); new reference solution added to improve determination of impurity A content; limits updated.

Impurity B: accuracy of mass and volume figures in solutions increased in accordance with current style for solutions for quantitative use.

Impurities: section updated; new unspecified impurity added.

Griseofulvin (0182)

Definition: production restricted to the use of certain strains of *Penicillin griseofulvum* by removal of the phrase "or obtained by any other means" and by revision of the content limits.

Characters: particle size limits removed as they relate to finished product requirements and should therefore not be included; statement on polymorphism added.

Identification: test B removed as identification by IR considered sufficient.

Related substances: GC method replaced by LC with the introduction of a limit for total impurities based on batch data.

Substances soluble in light petroleum: test removed as control of this aspect should be addressed in the manufacturing process controls.

Assay: LC method introduced to replace the use of specific absorbance.

Impurities: section introduced to include specified impurities.

Human haematopoietic stem cells (2323)

Water: following the suppression of the Ph. Eur. monograph *Water, highly purified (1927)* from Supplement 9.7, which is now fully covered by the revised monograph *Water for injections (0169)*, the reference to this monograph has been deleted.

Microbiological control: title of general chapter 2.6.27, revised in Supplement 9.2, updated.

Indometacin (0092)

Characters: note concerning polymorphism added.

Identification B: use of volumetric solutions avoided.

Related substances: method optimised to improve selectivity and application of gradient.

Assay: grade of water used in solvent mixture amended in accordance with the Technical Guide (2015).

Miconazole (0935)

Identification: IR sample preparation deleted; 2nd identification series modified to avoid use of dioxan (former test C).

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

Miconazole nitrate (0513)

Identification: 2nd identification series modified to avoid use of dioxan (former test C).

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

Mupirocin (1450)

Related substances: reference solution (c) removed as it was superfluous and was not required to perform the test.

Related substances, Assay: grade of solvents amended in accordance with the Technical Guide (2015).

Mupirocin calcium (1451)

Related substances: reference solution (c) removed as it was superfluous and was not required to perform the test.

Related substances, Assay: grade of solvents amended in accordance with the Technical Guide (2015).

Nicergoline (1998)

Related substances: quantitative expression of acceptance criteria introduced.

Norfloxacin (1248)

Characters: statement on polymorphism added.

Identification: recrystallisation procedure added as substance shows polymorphism.

Related substances: former solution A now called solvent mixture, and grade of water in mobile phase A amended in accordance with the Technical Guide (2015).

Nortriptyline hydrochloride (0941)

Identification B: clarification regarding dissolution of the precipitate.

Related substances: new reference solutions added to improve determination of impurity A content; grades of solvents amended in accordance with the Technical Guide (2015).

Poloxamers (1464)

Functionality-related characteristics (FRCs): this section has been added. The different types of poloxamer are used as vehicle, viscosity-increasing agent, wetting agent, solubilising agent, dispersing agent, suspending agent. Depending on the different uses, FRCs comprise viscosity, particle-size distribution, oxypropylene:oxyethylene ratio and gel formation.

Polymyxin B sulfate (0203)

The microbiological assay (2.7.2) has been re-instated and the former HPLC assay method has been converted to a test for composition. In this way the monograph is harmonised with the monograph *Colistin sulfate (0320)*, which also consists of a mixture of polypeptide sulfates and enables the expression of content in International Units.

The following additional changes have been made:

Definition: means of production restricted to certain strains of *Paenibacillus polymyxa*.

Content: limit for minimum content, expressed in IU/mg, introduced.

Characters: solubility characteristics updated.

Identification B: revised to examine chromatograms obtained in test for composition.

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

Composition: test introduced with applicable limits.

Related substances: reporting threshold expressed quantitatively.

Labelling: section added.

Proguanil hydrochloride (2002)

Second identification: colour reaction (former test C) deleted.

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

Pyrimethamine (0288)

Identification D: TLC method updated.

Solution S: preparation updated.

Related substances: TLC replaced by LC and limits updated.

Impurities: section introduced.

Saccharin (0947)

Further to decisions taken at the September 2017 PDG meeting, this monograph has been withdrawn from the PDG work programme and consequently from chapter 5.8. It remains the ultimate responsibility of the user to verify the current content of the texts in force in the respective pharmacopoeias.

Saccharin sodium (0787)

Further to decisions taken at the September 2017 PDG meeting, this monograph has been withdrawn from the PDG work programme and consequently from chapter 5.8. It remains the ultimate responsibility of the user to verify the current content of the texts in force in the respective pharmacopoeias.

Sertraline hydrochloride (1705)

Enantiomeric purity: volume of reference solution (a) modified to lower the accuracy requirement; reagent used to describe stationary phase modified; sections for identification of impurities and for relative retention added.

Impurity E: volume of reference solution (b) modified to lower the accuracy requirement; grade of solvents amended in accordance with the Technical Guide (2015); section for identification of peaks added.

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

Simvastatin (1563)

Related substances: method optimised, now covering 6 additional impurities; limits updated.

Assay: method optimised in line with new related substances test.

Impurities: section updated.

Sodium molybdate dihydrate (1565)

Solution S: concentration lowered to 10 per cent.

Chlorides: method adapted to the new concentration of solution S.

Telmisartan (2154)

Related substances: current method allows control of 2 additional impurities; grades of solvents amended in accordance with the Technical Guide (2015); reagent used to describe stationary phase modified.

Impurities: section updated.

Temozolomide (2780)

Related substances: a more dilute test solution has been introduced for the assay.

Loss on drying: test replaced by coulometric Karl Fischer titration to allow a more accurate determination of water and to limit exposure to the substance, due to its toxicity.