Comments concerning texts published in Issue 12.1

Brief descriptions of the modifications that have been made to new, revised and corrected texts adopted by the European Pharmacopoeia Commission at the November session and published in Issue 12.1 are provided below. Please note that these descriptions are not provided systematically for new and corrected texts, but are instead provided on a case-by-case basis. This information is reproduced in the Knowledge database under View history.

All revised, corrected or deleted parts of a text published in the European Pharmacopoeia are indicated by change marks in the form of triangles.

GENERAL CHAPTERS

1. General notices

As a result of the transition of the European Pharmacopoeia to a solely online format from the 12th Edition, several changes to the way in which information about texts is displayed have been introduced in order to improve the user experience. Linked to this, the *General Notices* has undergone a minor revision to update the information about the organisation of the publication cycle and the general monographs.

1.1.1 General Principles: wording “edition or supplement” replaced by “issue” to reflect the terminology used to describe the new publication cycle where each edition is composed of three “issues”.

1.4 General monographs and general monographs on dosage forms: section 1.4 of the *General Notices* has been revised to define more clearly which monographs are considered “general monographs” and to improve the overall clarity of the section.

Separate to the changes driven by the new European Pharmacopoeia format, the following modification has also been made.

1.1.2.6 Pharmacopoeial harmonisation: wording revised to indicate that the Pharmacopoeial Discussion Group (PDG) has more than 3 members.

2.2.39. Molecular mass distribution in dextrans

System suitability: criteria revised from fixed ranges to relative ranges around the assigned value of the CRS; CRSs used for system suitability replaced in line with revised criteria.

2.5.42. *N*-Nitrosamines in active substances and medicinal products

Inclusion of sartan-containing medicinal products in the scope of procedures A and C, and procedure A can be applied as a quantitative test. Addition of the requirement for performing a validation when a procedure is modified beyond the allowable adjustments of chromatographic conditions listed in *Chromatographic separation techniques* (*2.2.46*).

2.9.34. Bulk density of powders

This minor revision corresponds to Revision 4, Correction 2 (based on the Pharmacopoeial Discussion Group (PDG) working procedure) within the Pharmacopoeial harmonisation process. The coordinating pharmacopoeia is the Ph. Eur.

Compared to the general chapter published in Supplement 11.5 of the Ph. Eur., the following changes are proposed:

Tapped bulk density section:

- titles of Method 1 and Method 2 changed by adding ‘high drop' and ‘low drop' to clearly identify the two methods;

- Figure 3: inclusion of both drop heights as per Method 1 and Method 2;

- ‘Dimensions in millimetres' deleted from below the caption of Figure 3 as dimensions given in the figure itself;

- Method 2: significant figure added for the drop (from ‘3' to ‘3.0') to indicate the necessary precision.

5.1.9. Guidelines for using the test for sterility

The revised general chapter allows the use of alternative methods according to general chapter *5.1.6. Alternative methods for control of microbiological quality*.

In the Precautions against microbial contamination section, the classification for a laminar-air-flow cabinet and its location have been removed because this type of information is usually not defined in the Ph. Eur. and is described in other relevant documents (e.g. Annex 1 of the *EudraLex - Volume 4: Good manufacturing practice*).

The line stating that the sterility test is the only analytical method available to the authorities has been removed.

Sampling plan considerations have been completed in order to also provide recommendations for terminally sterilised products and lyophilised products.

Recommendations for sterility test invalidation are no longer limited to condition (d) of general chapter *2.6.1. Sterility*.

Editorial changes have been made throughout the text for greater clarity.

Editorial modification of the French title from “*Indications sur l’application de l’essai de stérilité*” to “*Recommandations pour la réalisation de l’essai de stérilité*”.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs.

VACCINES FOR VETERINARY USE

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

Immunogenicity:

- the validity criterion and animal welfare statement for the PD_{50} and PPG tests have been separated for greater clarity;

- the wording of the validity criterion for the above-mentioned tests has been clarified ("lesions at sites other than the tongue" replaced by a reference to lesions on the feet). This is to reflect the current practice of EU FMD Reference Laboratories and FMD vaccine manufacturers, which do not score the lesions on the head. Indeed, mouth lesions may be caused by local spread of the virus from the inoculation site and are not necessarily reflective of generalised infection; they should not therefore be recorded.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Adhatoda vasica leaf (2738)

Assay: methanol content in the test and reference solutions reduced to avoid artefacts and improve shape of peak due to vasicine.

Fleeceflower root (2433)

Definition: botanical name updated.

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

Identification C: analytical procedure improved, harmonised with that of *Polygonum multiflorum stem (2725)* and aligned with general chapter *2.8.25*.

Assay: grade of solvents used in the mobile phase amended in accordance with the Technical Guide (2022).

Fourstamen stephania root (2478)

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

Identification C: analytical procedure improved and aligned with general chapter *2.8.25*.

Assay: grades of solvents used in the mobile phase amended in accordance with the Technical Guide (2022).

Wild pansy (flowering aerial parts) (1855)

Identification: macroscopic description updated; illustration of powdered herbal drug introduced and its legend integrated into text; TLC replaced by high-performance thin-layer chromatography (HPTLC) in accordance with general chapter *2.8.25*.

Loss on drying: limit tightened based on batch data.

Cadmium: maximum limit increased based on batch data.

Assay: unspecific absorbance assay replaced by more specific HPLC.

HOMOEOPATHIC PREPARATIONS

Homoeopathic preparations: introduction (90006)

Homoeopathic preparations: introduction has been corrected to remove the reference to “general monographs”, as from 12.1 the homoeopathic general monographs are no longer located in section 13 Homoeopathic preparations but instead in section 06 General monographs *(Homoeopathic preparations (1038), Herbal drugs for homoeopathic preparations (2045), Mother tinctures for homoeopathic preparations (2029), Methods of preparation of homoeopathic stocks and potentisation (2371))* and section 07 Dosage forms (*Pillules for homoeopathic preparations (2153), Homoeopathic pillules, impregnated (2079) and Homoeopathic pillules, coated (2786)*).

MONOGRAPHS

Aluminium hydroxide, hydrated, for adsorption (1664)

Sedimentation: the wording has been modified to clarify the requirements.

Nitrates: in terms of the colour produced, the analytical procedure is not able to discriminate between amounts greater than 1 µg; the preparation of the solution has been modified to correct this issue.

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), it is proposed to delete the test.

Amitriptyline hydrochloride (0464)

First identification: tests relabelled due to addition of the second identification sub-section.

Second identification: sub-section added since the substance is used in pharmacies.

Related substances: grades of solvents amended in accordance with the Technical Guide (2022).

Amlodipine besilate (1491)

Impurity I: new LC procedure to control this additional impurity.

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

Aprotinin (0580)

Molecular weight: corrected to align with *Aprotinin concentrated solution (0579)*.

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an*

era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur. Pharmeur Bio Sci Notes. 2024:12-26).

Aprotinin concentrated solution (0579)

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Bromperidol decanoate (1397)

Related substances: additional experimental verification revealed that the elution order of the late eluting impurities D, K and E was incorrect (impurity D eluting before impurities K and E); impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; system suitability criterion amended to take into account the most critical pairs and the correct elution order of the impurities.

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

Butylhydroxytoluene (0581)

Definition: content limits added.

Characters: solubility in heptane added.

Identification: former first identification tests replaced by state-of-the-art analytical procedures (IR and a test cross-referencing the assay); in second identification, the three tests have been replaced by a TLC procedure based on the TLC method originally described for related substances, that can discriminate between butylhydroxytoluene and butylhydroxyanisole.

Freezing point: test deleted as it has become obsolete with the introduction of a test for purity based on LC instead of TLC.

Related substances: former TLC method replaced by new UHPLC-UV method covering 11 new impurities.

Water: test introduced.

Assay: added.

Impurities: section introduced in accordance with the new test for related substances.

Charcoal, activated (0313)

Solution S: following the deletion of the analytical procedures used for copper, lead and zinc, this solution is no longer needed and has been deleted.

Copper, Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), these tests will be kept with the current limits. In addition, the following impurities will be added: cobalt (5 ppm), nickel (20 ppm) and vanadium (10 ppm); a certain degree of flexibility in the choice of method to be used has been introduced.

Zinc: the test will be kept with the current limit and a certain degree of flexibility in the choice of method to be used has been introduced.

Chymotrypsin (0476)

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Editorial changes have also been made throughout the monograph. Notably, the description of the colour was updated from purple to reddish-violet as per Style Guide.

Clomipramine hydrochloride (0889)

First identification: tests relabelled due to addition of the second identification sub-section.

Second identification: sub-section added since the substance is used in pharmacies.

Related substances: reagent used to describe the stationary phase modified; grade of water in the mobile phase amended in accordance with the Technical Guide (2022); in the preparation of reference solution (c), volume and mass expressed using fewer significant figures due to the qualitative use of this solution.

Clonazepam (0890)

Identification by IR: use of a reference standard as an alternative to reference spectrum.

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; only impurity B is now specified at 0.10%; the system suitability criterion has been modified to avoid the use of an external compound.

Clopidogrel besilate (2790)

Identification: the ratio between the peaks due to besilate and clopidogrel in test D has been deleted, as the main peak has been found to be outside the linear range of the UV-detector. The requirement for similar retention time of the peaks due to besilate in the test and reference solutions has been considered sufficient to properly identify the besilate ions.

Enantiomeric purity: in the preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution.

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

Clopidogrel hydrogen sulfate (2531)

Enantiomeric purity: in the preparation of test solution, mass expressed using more significant figures for better accuracy; calculation method updated to reflect the manufacturer's approach; system suitability test updated for the signal-to-noise ratio to verify the sensitivity of the procedure.

Related substances: in the preparation of test solution, mass expressed using more significant figures for better accuracy.

Codergocrine mesilate (2060)

Assay: for the calculation of codergocrine mesilate content, correction factors updated to better reflect the difference in absorption coefficient between dihydroergocristine mesilate and the 3 other components.

Danaparoid sodium (2090)

Structural formula: modified to simplify labelling of substituents (from R1-6 to R and R′).

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

The sentence referring to minimising or eliminating endotoxins has also been deleted. This aspect is addressed in the Tests section.

Daunorubicin hydrochloride (0662)

Production: the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Dicloxacillin sodium monohydrate (0663)

Production: as some manufacturers may choose not to use *N*,*N*-dimethylaniline in their production process anymore, the presence of this impurity is now controlled using a risk-based approach. As this aspect cannot always be verified by an independent analyst, the requirement for testing *N*,*N*-dimethylaniline has been removed from the Tests section and a Production section has been introduced.

Specific optical rotation: the test has been removed as the quality is adequately controlled with the improved method for related substances.

Related substances: an improved LC method is proposed with limits based on the quality of the substance used in the manufacture of currently approved products.

N,N-dimethylaniline: see Production section above.

Assay: a revised method has been introduced based on the improved LC method used for related substances.

Impurities: additional impurities have been included and structures modified based on currently available data.

Dosulepin hydrochloride (1314)

First identification: tests relabelled due to changes in the second identification.

Second identification: former test A (by UV) deleted since not feasible in pharmacies; former test C (colour reaction) deleted as considered superfluous; new test B (by TLC with double detection) introduced.

Escitalopram (2758)

Related substances: grades of solvents amended in accordance with the Technical Guide; in the preparation of test solution, mass expressed using more significant figures for better accuracy; in the preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution.

Enantiomeric purity: grades of solvents amended in accordance with the Technical Guide; in the preparation of reference solution (a), mass and volumes expressed using fewer significant figures due to the qualitative use of this solution; calculation method updated to reflect the manufacturer's approach; reporting threshold replaced by an additional system suitability test (minimum signal-to-noise ratio) to verify the sensitivity of the procedure.

Escitalopram oxalate (2733)

Related substances: grades of solvents amended in accordance with the Technical Guide; in the preparation of test solution, mass expressed using more significant figures for better accuracy; in the preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution.

Enantiomeric purity: grades of solvents amended in accordance with the Technical Guide; in the preparation of reference solution (a), mass and volumes expressed using fewer significant figures due to the qualitative use of this solution; calculation method updated to reflect the manufacturer's approach; reporting threshold replaced by an additional system suitability test (minimum signal-to-noise ratio) to verify the sensitivity of the procedure.

Esomeprazole magnesium dihydrate (2787)

Enantiomeric purity: grades of solvents amended in accordance with the Technical Guide; in the preparation of the test solution, mass expressed using more significant figures for better accuracy; in the preparation of reference solution (a), volumes expressed using fewer significant figures due to the qualitative use of this solution; calculation method updated to reflect the manufacturer’s approach; system suitability test introduced for the signal-to-noise ratio to verify the sensitivity of the procedure.

Related substances: in the preparation of the test solution, mass expressed using more significant figures for better accuracy; in the preparation of reference solutions (a) and (b), volumes expressed using fewer significant figures due to the qualitative use of these solutions.

Esomeprazole magnesium trihydrate (2372)

Enantiomeric purity: grades of solvents amended in accordance with the Technical Guide; in the preparation of the test solution, mass expressed using more significant figures for better accuracy; in the preparation of reference solution (a), volumes expressed using fewer significant figures due to the qualitative use of this solution; calculation method updated to reflect the manufacturer's approach; system suitability test introduced for the signal-to-noise ratio to verify the sensitivity of the procedure.

Related substances: in the preparation of the test solution, mass expressed using more significant figures for better accuracy; in the preparation of reference solutions (a) and (b),

volumes expressed using fewer significant figures due to the qualitative use of these solutions.

Esomeprazole sodium (2923)

Enantiomeric purity: in the preparation of the test solution, mass expressed using more significant figures for better accuracy; calculation method updated to reflect the manufacturer's approach; reporting threshold replaced by an additional system suitability test (minimum signal-to-noise ratio) to verify the sensitivity of the procedure.

Related substances: in the preparation of the test solution, mass expressed using more significant figures for better accuracy.

Fluconazole (2287)

Related substances: the quantitative style has been introduced; limits for impurities B and C were updated to reflect the quality of the substances in approved medicinal products on the European market; the description of the stationary phase has been amended.

Fluticasone propionate (1750)

Related substances: the description of reference solution (c) has been changed due to a change in the preparation of the CRS for system suitability.

Follitropin (2285)

Assay: the procedure has been modified to remove the mercury-containing compound thiomersal (REACH) as an example of a suitable antimicrobial preservative.

Follitropin concentrated solution (2286)

Assay: the procedure has been modified to remove the mercury-containing compound thiomersal (REACH) as an example of a suitable antimicrobial preservative.

Glycerol dibehenate (1427)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Glycerol distearate (1428)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Glycerol monolinoleate (1429)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Glycerol mono-oleate (1430)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Glycerol monostearate 40-55 (0495)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Gonadotrophin, chorionic (0498)

Assay: the procedure has been modified to remove the mercury-containing compound thiomersal (REACH) as an example of a suitable antimicrobial preservative.

Haemodialysis, concentrated solutions for (3206)

This monograph has been elaborated specifically for concentrated solutions for haemodialysis because they are no longer covered by monograph *0128* which, subsequent to its proposed revision, now describes requirements for final solutions for haemodialysis only.

Haemodialysis solutions, concentrated, water for diluting (1167)

The monograph has been revised to reflect current practices and to align with the water monographs (*Water, purified (0008)* and *Water for injections (0169)*).

- *Definition section*: updated to clearly define how the preparation / solution is prepared.

- *Production section*: added:

- Use of both potable water and water prepared by ion exchange or distillation no longer described to reflect most common current practices.

- Paragraph on the “surveillance of the quality of water… and analytical methods” moved to the Tests section.

- Microbial contamination test renamed “Microbiological monitoring” and moved from Tests section to Production section. The R2A agar test procedure is described and includes the following parameters: medium, time and temperature, as well as preparation of test strains and growth promotion of R2A agar.

- *Tests section:*

- *Aluminium*: replaced by a more state-of-the-art method which is already included in the other dialysis monographs.

- *Heavy metals*: Heavy metals test (*2.4.8*) removed and replaced by an Other elemental impurities test describing the individual metal tests (copper and lead, with applicable limits, and additional elemental impurities) based on a risk assessment approach.

Bacterial endotoxins: the text now allows the use of the recombinant factor C (rFC) test for the control of bacterial endotoxins.

Haemodialysis, solutions for (0128)

The previous version of this monograph described both concentrated and final solutions for haemodialysis. The revised monograph focuses exclusively on final solutions. Consequently, major changes have been made to the Definition, Tests and Labelling sections.

- Definition section:

- Updated to cover both solutions prepared on-line and provided in containers.

- Formulation composition tables: addition of the use of citrate and citric/lactic acids and correction of the concentration range (potassium, acids) to reflect the current products on the market.

- Addition of a statement about the use of antioxidants.

- Identification section: addition of citrates.

- Tests section:

- Inclusion of new tests (pH, Hydroxymethylfurfural, Particulate contamination and Citrate).

- Lactate and hydrogen carbonate assay has been added to offer possibility to perform both tests simultaneously in alignment with monograph *0861*.

- Assay section: inclusion of the citrate assay.

Haemofiltration and haemodiafiltration, concentrated solutions for (2770)

The monograph has been revised to reflect current practices and to align it with other dialysis monographs (i.e. *0128*, *0861*, *0862*):

- Definition section:

- Addition of a definition of the final and ready-to-use solutions.

- Addition of a statement about the three types of concentrated solutions used.

- Removal of the table giving the composition of the concentrated formulations and making reference to *Haemofiltration and haemodiafiltration, solutions for (0861)*.

- Removal of the statement on the use of hydrogen carbonate, which does not apply to haemofiltration and haemodiafiltration concentrated solutions.

- Clarification for the statement about the use of antioxidants.

- Identification section: removal of carbonates and hydrogen carbonates, which is specific to ready-to-use haemofiltration and haemodiafiltration solutions.

- Tests section:

- pH: addition of clarification that the limits apply to ready-to-use solutions; adding new limits when the solution contains hydrogen carbonate.

- Aluminium: addition of clarification that the limit applies to final solutions.

- Hydroxymethylfurfural: clarification that this test applies when the preparation contains glucose and is heat-sterilised.

–Microbial contamination: inclusion of new test parameter when the preparation is not claimed to be sterile.

- Pyrogenicity: addition of new test in accordance with the new requirement in general chapter *5.1.13*.

Haemofiltration and haemodiafiltration, solutions for (0861)

The monograph has been revised to reflect current practices and to align with the other dialysis monographs (i.e. *0128*, *0862* and *2770*):

- *Definition section*:

- Addition of a statement on the on-line preparation by diluting concentrated solutions and clarification between the on-line preparations and ready-to-use preparations/solutions.

- Addition of a statement about the use of antioxidants.

- *Formulation compositions table:* addition of the use of citrate/citric acid.

- *Identification section*: Addition of citrates since citrate has been added as a component of the haemofiltration and haemodiafiltration preparations.

- *Tests section*:

- *Hydroxymethylfurfura*l: addition of the clarification that this test applies when (a) the solution is provided in containers, contains glucose and is heat-sterilised, or (b) the solution is prepared on-line and is produced from heat-sterilised concentrates containing glucose.

- *Extractable volume*: addition of clarification that this test applies to solutions packaged in containers.

- *Assay section*: inclusion of the citrate assay since citrate has been added as a component of the haemofiltration and haemodiafiltration preparations.

- *Labelling section*: addition of the requirement that the haemofiltration and haemodiafiltration solution is sterile.

Hard fat (0462)

Hydroxyl value: possibility of performing the titration on a warmed solution introduced to avoid potential congealing.

Hard fat with additives (2731)

Hydroxyl value: possibility of performing the titration on a warmed solution introduced to avoid potential congealing.

Heparin calcium (0332)

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia, (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Heparin sodium (0333)

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Heparins, low-molecular-mass (0828)

Identification C: the preparation of the reference solution was adapted taking into account the amount of *heparin low-molecular-mass for calibration CRS* 6 per vial.

Homatropine hydrobromide (0500)

Characters: melting point deleted.

Related substances: grades of solvents amended in accordance with the Technical Guide; in the preparation of reference solution (b), volume expressed using fewer significant figures due to the qualitative use of this solution; requirement for the symmetry factor deleted; quantitative style now prescribed; introduction of a limit at 0.10 per cent for unspecified impurities; impurity limits updated to reflect current quality of the products on the market: impurities A, B, C and D listed as unspecified impurities; limit for total impurities tightened from 1.0 per cent to 0.5 per cent.

Hydroxyethylcellulose (0336)

Functionality-related characteristics: the section has been revised to add, in addition to its use as a viscosity-increasing agent, the following characteristics that may be considered critical and useful material attributes when hydroxyethylcellulose is used as a matrix former for modified-release solid dosage forms: viscosity and molar substitution (cross-references); molecular mass distribution, particle-size distribution and powder flow (references to Ph. Eur. general chapters). The term ‘degree of substitution’ has been replaced by ‘molar substitution’.

The entire non-mandatory Functionality-related characteristics section is marked with white diamonds to indicate its status as a local Ph. Eur. requirement of this PDG harmonised monograph.

Hydroxypropylcellulose, low-substituted (2083)

Assay: calculation updated to align with the PDG sign-off text.

Hypromellose (0348)

Assay: calculation updated to align with the PDG sign-off text.

Indometacin (0092)

Characters: solubility in heptane added.

Related substances: concentration of formic acid in mobile phases A and B corrected in accordance with the procedure as originally validated during elaboration of the monograph.

Assay: concentration of acetic acid in mobile phases A and B corrected by referring to the right reagent, thus in accordance with the procedure as originally validated during elaboration of the monograph.

Kanamycin acid sulfate (0033)

Formula: the chemical structure has been introduced.

Definition: the chemical nomenclature has been introduced. The definition now shows that the substance may contain a variable quantity of sulfuric acid and water, and that it is produced from kanamycin monosulfate monohydrate.

Production: the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an*

era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur. Pharmeur Bio Sci Notes. 2024:12-26).

Kanamycin monosulfate monohydrate (0032)

Production: the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Lacosamide (2992)

Enantiomeric purity: in the preparation of reference solutions (a) and (b), volumes expressed using fewer significant figures due to the qualitative use of these solutions; calculation method updated to reflect the manufacturer's approach; reporting threshold replaced by an additional system suitability test (minimum signal-to-noise ratio) to verify the sensitivity of the procedure.

Related substances: in the preparation of reference solutions (c) and (d), volumes expressed using fewer significant figures due to the qualitative use of these solutions.

Lamivudine (2217)

Enantiomeric purity: in the preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution; calculation method updated to reflect the manufacturer's approach; system suitability test introduced for the signal-to-noise ratio to verify the sensitivity of the procedure.

Impurities: structures and nomenclatures updated.

Levetiracetam (2535)

Enantiomeric purity: in the preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution; calculation method updated to reflect the manufacturer's approach; reporting threshold replaced by an additional system suitability test (minimum signal-to-noise ratio) to verify the sensitivity of the procedure.

Impurity G: in the preparation of the test solution, mass expressed using more significant figures for better accuracy; in the preparation of the test solution (c), volumes expressed using fewer significant figures due to the qualitative use of this solution.

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

Macrogols (1444)

Functionality-related characteristics: the section has been revised to add, in addition to its use as a solvent, stabiliser, lubricant, thickener and base, the following characteristics that may be considered critical and useful material attributes when macrogols are used as a binder and as a matrix former for modified-release solid dosage forms:

- for macrogols used as a binder: viscosity (cross-reference);

- for macrogols used as a matrix former for modified-release solid dosage forms: viscosity (cross-reference); molecular mass distribution, particle-size distribution and powder flow (references to Ph. Eur. general chapters).

Few editorial changes have also been made throughout the monograph to align with the current style guide.

Macrogols, high-molecular-mass (2444)

Functionality-related characteristics: a section has been added to introduce characteristics that may be considered critical and useful material attributes when high-molecular mass macrogols are used as a binder and as a matrix former for modified-release solid dosage forms:

- for high-molecular-mass macrogols used as a binder: viscosity (cross-reference);

- for high-molecular-mass macrogols used as a matrix former for modified-release solid dosage forms: viscosity (cross-reference); molecular mass distribution, particle-size distribution and powder flow (references to Ph. Eur. general chapters).

Maize starch (0344)

This draft corresponds to Revision 4, Stage 2 (based on the Pharmacopoeial Discussion Group (PDG) working procedure) within the Pharmacopoeial harmonisation process. The coordinating pharmacopoeia is the USP. The original text submitted to the PDG is published in the Pharmacopoeial harmonisation section.

Compared to the monograph published in the 11th Edition of the Ph. Eur., the following changes are proposed:

Identification: limits for the diameters of both angular polyhedral granules and rounded/spheroidal granules revised to a maximum of about 35 µm based on the distribution of granule diameters and shapes found by testing maize starch from multiple manufacturers.

Methylcellulose (0345)

Assay: calculation updated to align with the PDG sign-off text.

Nicotine ditartrate dihydrate (2599)

Specific optical rotation: concentration of the solution and range updated; value calculated on the anhydrous substance.

Related substances: *water for chromatography R* used for the preparation of the mobile phase; in the preparation of the test solution, mass expressed using more significant figures; in the preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution.

Nitrendipine (1246)

Related substances: the quantitative style has been introduced; the limit of impurity C was updated; impurity A is now specified at 0.10%. These changes reflect the quality of the substances in approved medicinal products on the European market.

Oxytetracycline hydrochloride (0198)

Related substances: *dilute hydrochloric acid R1* has been replaced by the stronger *dilute hydrochloric acid R* in order to reduce the volume of reagent required to perform the pH adjustment of the oxalic acid solution used in the solvent mixture.

Pentobarbital sodium (0419)

First identification: tests relabelled due to addition of the second identification sub-section.

Second identification: sub-section added since the substance is used in pharmacies.

Peritoneal dialysis, solutions for (0862)

The monograph has been revised to reflect current practices and to align with the other dialysis monographs (*0128*, *0861* and *2770*):

- *Tests section*: *Hydroxymethylfurfural*: addition of clarification that the test is carried out only when the glucose-containing solution is heat-sterilised.

- *Labelling section*: addition of the requirement that the peritoneal dialysis solution is sterile.

Pivmecillinam hydrochloride (1359)

Related substances: the preparation of reference solution (c) has been amended to take into account the new lyophilised form of *pivmecillinam impurity C CRS*.

Propylene glycol dilaurate (2087)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Propylene glycol monocaprylate (2799)

Assay: column diameter changed from 7.0 mm to 7.5 mm. Columns with a diameter of 7.0 mm are no longer manufactured.

Propylene glycol monolaurate (1915)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Remifentanil hydrochloride (2644)

Characters: in view of feedback from users, the reference to solubility in acetonitrile has been deleted.

Identification by IR: the use of a reference spectrum has been added as an alternative to the reference standard.

Methyl acrylate: *water for chromatography R* has been replaced by an apolar solvent for the preparation of the test solution to avoid in-situ formation of methyl acrylate; the method parameters have been adjusted accordingly.

Rifamycin sodium (0432)

Production: the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Rivaroxaban (2932)

Enantiomeric purity: in the preparation of the test solution, mass and volume expressed using more significant figures for better accuracy; calculation method moved up; system suitability test introduced for the signal-to-noise ratio to verify the sensitivity of the procedure.

Ropivacaine hydrochloride monohydrate (2335)

Enantiomeric purity: calculation method updated to reflect the manufacturer's approach; grade of water used amended in accordance with the Technical Guide; in the preparation of the test solution, mass and volume expressed using more significant figures for better accuracy; in the preparation of reference solution (b), masses expressed using fewer significant figures due to qualitative use of this solution; migration time of ropivacaine and relative migration of impurity G included.

Related substances: grades of solvents amended in accordance with the Technical Guide; in the preparation of the test solution, mass and volume expressed using more significant figures for better accuracy.

Rotigotine (3014)

Enantiomeric purity: calculation method moved up; additional system suitability test (signal-to-noise ratio) introduced to verify the sensitivity of the procedure; in the preparation of test solution, mass and volume expressed using more significant figures for better accuracy.

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

Salicylic acid (0366)

Solution S: preparation transferred in the only test in which it is used, the test for chlorides.

Related substances: column length decreased reflecting the dimensions of the particular column used in the validation of the proposed optimised procedure; grade of water used in the mobile phase amended in accordance with the Technical Guide (2022); quantitation of impurities optimised, carried out versus a 0.05 per cent impurity B solution; injection volume decreased 5 fold and concentration of the test solution increased 10 fold to achieve sufficient sensitivity; first system suitability test acceptance criterion based on a minimum signal-to-noise ratio for a 0.05 per cent diluted test solution to ensure the detection of unknown impurities structurally-close to the API, since the detector response for the API is lower than the detector response for impurity B which is used to quantitate all impurities; second system suitability test acceptance criterion widened based on recent experimental results injecting the proposed corresponding reference solution; limits expressed in the quantitative style.

Assay: colorimetric end-point detection replaced by more accurate and precise potentiometric end-point detection.

Impurities: section updated in accordance with the limits in the test for related substances.

Sitagliptin phosphate monohydrate (2778)

Identification C: sample size and volume of solvent expressed using fewer significant figures due to qualitative use of this test.

Enantiomeric purity: in the preparation of the test solution, sample size expressed with one more significant figure due to its use in the preparation of reference solution (a), which is used for a quantitative test (signal-to-noise ratio); calculation method updated to reflect the manufacturer's approach; reporting threshold replaced by an additional system suitability test (minimum signal-to-noise ratio) to verify the sensitivity of the procedure.

Sodium hydrogen carbonate (0195)

Ammonium: based on new data, preparation of solutions amended to bring to a strongly alkaline pH.

Sodium polystyrene sulfonate (1909)

Definition: amended to clarify that the monograph covers a sodium sulfonated copolymer of styrene and divinylbenzene, which has very different properties from the sodium sulfonated polystyrene homopolymer; structure added.

Styrene: more accurate quantities mentioned; run time, retention time and chromatogram added; grade of solvent for mobile phase and reagent used to describe the stationary phase amended.

Starch, hydroxypropyl (2165)

Identification A: Maize-based hydroxypropyl starch criteria revised in-line with the revision to the *Maize starch (0344)* monograph.

Starches, hydroxyethyl (1785)

Molecular weight (Mw) and molecular weight distribution: system suitability criteria widened in order to better reflect the variability in the method reported by several laboratories; unit specified (daltons); test name revised to 'Molecular mass (*Mw*) and molecular mass distribution' to accurately describe the value measured by the test (English text only).

Editorial changes have also been made throughout the monograph to align with the current style guide.

Streptomycin sulfate (0053)

Production: the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Editorial changes have also been made throughout the monograph.

Sucrose monopalmitate (2319)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Sucrose stearate (2318)

Assay: column diameter changed from 7 mm to 7.5 mm. Columns with a diameter of 7 mm are no longer manufactured.

Tapentadol hydrochloride (3035)

Identification by IR: reference spectrum added as an alternative to chemical reference substance.

Enantiomeric purity: calculation method moved up; reporting threshold replaced by an additional system suitability test (minimum signal-to-noise ratio) to verify the sensitivity of the procedure.

Tobramycin (0645)

Production: the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Trypsin (0694)

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Editorial changes have also been made throughout the monograph (French version only).

Urofollitropin (0958)

Assay: the procedure has been modified to remove the mercury-containing compound thiomersal (REACH) as an example of a suitable antimicrobial preservative.

Urokinase (0695)

Production: a part of the section has been deleted in accordance with the strategy to remove animal tests for histamine and depressor substances and the remainders of these tests from the European Pharmacopoeia (see Bratos M, Kolaj-Robin O, Antoni M, Charton E. *Ph. Eur. testing for histamine and depressor substances using guinea-pigs and cats: the end of an era. Strategy for removal of animal tests for histamine and depressor substances and their vestiges from the Ph. Eur.* Pharmeur Bio Sci Notes. 2024:12-26).

Editorial changes have also been made throughout the monograph.

Ursodeoxycholic acid (1275)

Identification: TLC method description included under identification B (second identification) since the previously cross-referenced procedure for impurity C by TLC has been replaced by a new LC procedure.

Impurity C: TLC changed to LC procedure covering the control of additional impurity J.

Related substances: in the preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution; reagent used to describe stationary phase modified; tolerance for the column temperature changed from ± 1 °C to ± 2 °C; quantitative style now prescribed.

Impurities: impurity J introduced.

Zanamivir hydrate (2611)

Loss on drying: the test by loss on drying was reported to be inadequate to release all the water due to the crystalline structure of zanamivir; change to a micro determination method (evaporation technique) to allow a more accurate determination of the water content.