Comments concerning revised texts published in Supplement 10.4

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the March 2020 session and published in Supplement 10.4.

When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.4. 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

2.5.29. Sulfur dioxide

The nomenclature of glassware has been corrected. The structure and the wording of the chapter have also been edited.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include new monographs published in Supplement 10.4.

5.25. Process analytical technology

Text updated to introduce the newly elaborated chapter *5.28* on Multivariate statistical process control.

GENERAL MONOGRAPHS

Immunosera for human use, animal (0084)

Animal tests. Introduction of a paragraph fostering the use of humane endpoints in animal methods, and the replacement by alternative methods that may offer improvements in terms of animal welfare. The paragraph also includes a cross-reference to general chapter *5.2.14* on the Substitution of *in vivo* method(s) by *in vitro* methods for the quality control of vaccines.

Products of fermentation (1468)

Down-stream processing: Histamine and biogenic amines added to the list of substances to be reduced to a minimum or removed.

VACCINES FOR VETERINARY USE

Rabies vaccine (inactivated) for veterinary use (0451)

Batch potency test (section 2-4-4). Section revised to refer more explicitly to immunosorbent assays.

RADIOPHARMACEUTICAL PREPARATIONS

Sodium iodide (^{131}I) solution (0281)

Production. Preparations to which carrier iodide had been added are no longer excluded. Compliance with the test for iodide demonstrates a sufficiently low level of iodide in the preparation, independent of its origin.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Baical skullcap root (2438)

Identification A: section improved.

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

Feverfew (1516)

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

Assay:

– *parthenolide reagent replaced by corresponding CRS;*

– *grades of solvents amended in accordance with Technical Guide (2015).*

Sanguisorba root (2385)

Characters: section deleted.

Identification A: section improved.

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

Zanthoxylum bungeanum pericarp (2656)

Identification A: improved description.

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

MONOGRAPHS

Aciclovir (0968)

Related substances: specifications updated; system suitability criterion modified.

Bacterial endotoxins: test deleted as the requirement is covered by the general monograph *Substances for pharmaceutical use (2034)*.

Aluminium phosphate, hydrated (1598)

Soluble phosphates: concentration of Reference solution (a) corrected to correspond to the limit.

Ammonium chloride (0007)

Identification A: reaction (b) deleted to avoid the use of toxic reagent (REACH, potassium dichromate) and reaction (a) is considered to be sufficient.

Aprotinin (0580)

Assay: adjustment of preparation of Tryspin solution in order to take into account potential activity differences in future Trypsin BRP batches.

Aprotinin concentrated solution (0579)

Assay: adjustment of preparation of Tryspin solution in order to take into account potential activity differences in future Trypsin BRP batches.

Aripiprazole (2617)

Production: addition of Production section for the control of genotoxic impurities.

Bacterial endotoxins: limit deleted, as the requirements are covered by the general monograph *2034 Substances for pharmaceutical use*. Refer to Ph. Eur. policy on bacterial endotoxins February 2015 (cf. Pharmeuropa Technical information).

Atorvastatin calcium trihydrate (2191)

Related substances: composition of reference solution (c) modified according to the replacement of individual impurities CRSs by a single new CRS; system suitability test acceptance criterion modified accordingly.

Benserazide hydrochloride (1173)

Identification: test B modified in order to avoid the use of potassium dichromate (REACH).

Benzylpenicillin (procaine) monohydrate (0115)

Related substances: introduction of a dedicated *procaine benzylpenicillin impurity F CRS* due to limited stability of impurity F in *procaine benzylpenicillin for peak identification CRS*.

Calcium lactate monohydrate (2117)

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

Calcium lactate pentahydrate (0468)

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

Calcium lactate trihydrate (0469)

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

Calcium pantothenate (0470)

Identification: current test C deleted, IR identification added and introduction of a second identification as the substance is used in pharmacies.

Related substances: separation improved by introducing a gradient.

Carbomers (1299)

Apparent viscosity: wording clarified.

Cellulose, microcrystalline (0316)

Functionality-related characteristics: loss on drying has been added because the water content influences the performance of the excipient e.g. with regard to flow or compaction properties. White diamonds have been added showing that this section is only present in the Ph. Eur. text.

Cellulose, powdered (0315)

Functionality-related characteristics: loss on drying has been added because the water content influences the performance of the excipient e.g. with regard to flow or compaction properties. White diamonds have been added showing that this section is only present in the Ph. Eur. text.

Chlorpromazine hydrochloride (0475)

Identification: former test A deleted since the performance of UV-Vis tests is deemed unfeasible for pharmacies; former test D modified in order to avoid the use of potassium dichromate (REACH).

Cyproheptadine hydrochloride 1.5-hydrate (0817)

Title: degree of hydration added.

Identification: test B modified in order to avoid the use of potassium dichromate (REACH).

Acidity: use of volumetric solution avoided.

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

Dexamethasone isonicotinate (2237)

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

Loss on drying: the wording has been aligned to conditions currently described in the general chapter *2.2.32*.

Dexpanthenol (0761)

IR identification: ATR can also be used, a statement has been added to clarify that the preparation method described applies only if recording in transmission mode.

Second identification: deletion of the test for specific optical rotation and colour reaction, new TLC method.

3-Aminopropanol (impurity A): TLC replaced by a titration.

Related substances: test added using a gradient LC method.

Assay: dioxan replaced by glacial acetic acid, end-point determined potentiometrically.

Impurities: section added.

Disopyramide (1006)

Content: reference to the anhydrous instead of the dried substance, due to the replacement of the loss on drying test.

Identification: former test A deleted since the performance of UV-Vis tests is deemed unfeasible for pharmacies.

Related substances: retardation factor of disopyramide added.

Loss on drying: test replaced by semi-micro determination of water.

Dosulepin hydrochloride (1314)

Identification: test D modified in order to avoid the use of potassium dichromate (REACH).

Erythromycin (0179)

Related substances: in the preparation of reference solution (d), volume is expressed using fewer significant figures due to the qualitative use of this solution; the limit for impurity M was lowered to maximum 0.4 per cent (“any other impurity”) in agreement with current batch data.

Identification: the infrared absorption spectrophotometry test has been updated following revision of chapter *2.2.32* in Supplement 9.8.

Fluticasone propionate (1750)

Related substances: additional specified impurities introduced; additional system suitability criterion introduced.

Gadobutrol monohydrate (2735)

Appearance of solution: test deleted from the monograph as it does not control any impurity and is not a stability indicator in accordance with the Technical Guide.

Gelatin (0330)

Revision signed off by PDG (Pharmacopoeial Discussion Group) within the framework of pharmacopoeial harmonisation. The JP monograph for Gelatin will now apply to both gelling and non-gelling grades.

Definition: text is now harmonised across all pharmacopoeias.

Functionality-related characteristics: white diamonds have been added showing that this section is only present in the Ph. Eur. text.

Hypromellose phthalate (0347)

Content/Nomenclature: phthaloyl changed to phthalyl.

Characters: solubility in acetone and toluene deleted.

Viscosity, Phthalyl groups: these tests are considered as harmonised within the Pharmacopoeial Harmonisation framework. To have the same legal status in the Ph. Eur. , the JP and the USP, they have been moved to Tests and Assay, respectively, and are referred to under Functionality-related characteristics.

Free phthalic acid: change to repeatability requirement.

myo-Inositol (1805)

Related substances: elution order and resolution requirements for system suitability test amended.

Insulin injection, isophane (0833)

Definition: deletion of the reference to bovine insulin following the suppression of the monograph on *Bovine insulin (1637)* from the Ph. Eur. (Supplement 10.1).

Insulin injection, soluble (0834)

Definition: deletion of the reference to bovine insulin following the suppression of the monograph on *Bovine insulin (1637*) from the Ph. Eur. (Supplement 10.1).

Insulin preparations, injectable (0854)

Definition, Assay and Labelling: deletion of the reference to bovine insulin and of the use of Bovine insulin CRS following the suppression of the monograph on *Bovine insulin (1637)* from the Ph. Eur. (Supplement 10.1).

Insulin zinc injectable suspension (0837)

Definition, Identification: deletion of the reference to bovine insulin following the suppression of the monograph on *Bovine insulin (1637)* from the Ph. Eur. (Supplement 10.1).

Insulin zinc injectable suspension (amorphous) (0835)

Definition: deletion of the reference to bovine insulin following the suppression of the monograph on *Bovine insulin (1637)* from the Ph. Eur. (Supplement 10.1).

Insulin zinc injectable suspension (crystalline) (0836)

Definition: deletion of the reference to bovine insulin following the suppression of the monograph on *Bovine insulin (1637)* from the Ph. Eur. (Supplement 10.1).

Levomepromazine hydrochloride (0505)

Identification: test D modified in order to avoid the use of potassium dichromate (REACH).

Acidity or alkalinity: use of volumetric solutions avoided.

Related substances: retardation factor of levomepromazine added.

Lorazepam (1121)

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

Loss on drying: the wording has been aligned with conditions described in the general chapter *2.2.32*.

Lovastatin (1538)

Content: reference to the anhydrous instead of the dried substance, due to the replacement of the loss on drying test.

Impurity E: grade of acetonitrile used in the preparation of solutions amended in accordance with Technical Guide (2015); in preparation of reference solution (b), volume expressed using fewer significant figures due to the qualitative use of this solution; reagent used to describe stationary phase modified.

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

Loss on drying: test replaced by semi-micro determination of water.

Magnesium aluminometasilicate (2854)

Functionality-related characteristics: a section has been added, particle-size distribution by laser diffraction and specific surface area have been included as FRCs for the use as glidant in tablets and capsules.

Mercuric chloride (0120)

Identification A: reaction (b) deleted to avoid the use of toxic reagent (REACH, potassium dichromate).

Norfloxacin (1248)

Content: reference to the anhydrous instead of the dried substance, due to the replacement of the loss on drying test.

Loss on drying: test replaced by semi-micro determination of water.

Paroxetine hydrochloride (2283)

Identification: identification C modified in order to avoid the use of potassium dichromate (REACH), test D referencing the test for enantiomeric purity added.

Impurity D: title of the test replaced by enantiomeric purity; in preparation of reference solution (b), volume expressed using fewer significant figures due to the qualitative use of this solution; reagent used to describe stationary phase modified; Identification of impurities and Relative retention sections introduced; second and third system suitability requirements deleted.

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

Assay: in preparation of reference solution (b), volume and mass expressed using fewer significant figures due to the qualitative use of this solution; Identification of peaks and Relative retention sections introduced; grade of water in mobile phase amended in accordance with Technical Guide (2015); system suitability test acceptance criterion expressed using an additional significant figure.

Paroxetine hydrochloride hemihydrate (2018)

Identification: test B directly cross-referencing the corresponding purity test; identification D modified in order to avoid the use of potassium dichromate (REACH).

Impurity D: title of the test replaced by enantiomeric purity; in preparation of reference solution (b) volume expressed using fewer significant figures due to the qualitative use of this solution; reference solution (c) deleted due to the change in identification test B; reagent used to describe stationary phase modified; Identification of impurities and Relative retention sections introduced.

Related substances: grade of water in mobile phase A amended in accordance with Technical Guide (2015); Identification of impurities and Relative retention sections introduced.

Assay: in preparation of reference solution (b), volume and mass expressed using fewer significant figures due to the qualitative use of this solution; Identification of peaks and Relative retention sections introduced; grade of water in mobile phase amended in accordance with Technical Guide (2015); system suitability test acceptance criterion expressed using an additional significant figure.

Piperacillin monohydrate (1169)

Title: updated to reflect the substance is a monohydrate as per the definition.

Definition: the lower limit for the content has been revised based on the new maximum limit set for total related substances.

Production: the requirement to evaluate the potential presence of *N*,*N*-dimethylaniline and to validate the production method to demonstrate that it is not detectable in the final product above the limit of 20 ppm (*2.4.26, Method A*) has been introduced.

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

Related substances: an improved gradient method has been introduced with limits added for several individually specified impurities in addition to a limit for total impurities.

N,N-dimethylaniline: the test has been removed and the control of this impurity is addressed under the new Production section.

Assay: a new HPLC method has been introduced.

Impurities: the section has been updated to provide additional information on impurities to the extent known.

Piperacillin sodium (1168)

Definition: the lower limit for the content has been revised based on the new maximum limit set for total related substances.

Production: the requirement to evaluate the potential presence of *N*,*N*-dimethylaniline and to validate the production method to demonstrate that it is not detectable in the final product above the limit of 20 ppm (*2.4.26, Method A*) has been introduced.

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

Related substances: an improved gradient method has been introduced with limits added for several individually specified impurities in addition to a limit for total impurities.

N,N-dimethylaniline: the test has been removed and the control of this impurity is addressed under the new Production section.

Bacterial endotoxins: the test has been removed based on Ph. Eur. policy.

Assay: a new HPLC method has been introduced.

Labelling: the section has been added.

Impurities: the section has been updated to provide additional information on impurities to the extent known.

Piracetam (1733)

Related substances: specifications updated to reflect the current quality of substances in approved medicinal products on the market; an explicit criterion for unspecified impurities introduced in accordance with the general monograph *Substances for pharmaceutical use (2034)* and taking into account the maximum daily dose (> 2 g/day).

Impurities: transparency list updated.

Potassium chloride (0185)

Identification A: reaction (b) deleted to avoid the use of toxic reagent (REACH, potassium dichromate).

Potassium hydrogen tartrate (1984)

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

Prednicarbate (1467)

Related substances: new specified impurity introduced.

Prednisolone (0353)

Identification: 2nd identification added as substance used in pharmacies.

Related substances: in preparation of reference solutions (a) and (b), volumes expressed using fewer significant figures due to qualitative use of solutions; grades of solvents amended in accordance with Technical Guide (2015); reagent used to describe stationary phase modified.

Promazine hydrochloride (1365)

Identification: test B excluded from first identification series since IR is able to discriminate promazine hydrochloride from other phenothiazines; test D modified in order to avoid the use of potassium dichromate (REACH).

Related substances: retardation factors of promazine and chlorprothixene added.

Storage: section updated.

Promethazine hydrochloride (0524)

Identification: test B excluded from first identification series since IR is able to discriminate promethazine hydrochloride from other phenothiazines; test D modified in order to avoid the use of potassium dichromate (REACH).

Related substances: in preparation of reference solution (c), volume expressed using more significant figures due to the quantitative use of this solution; reagent used to describe stationary phase modified; redundant second system suitability test criterion deleted.

Propyphenazone (0636)

Acidity or alkalinity: use of volumetric solutions avoided.

Related substances: in preparation of reference solution (b), volume expressed using fewer significant figures due to the qualitative use of this solution; grade of water in the mobile phase amended in accordance with Technical Guide (2015); Identification of impurities section added.

Assay: mass of substance required reduced and use of ethylene chloride (REACH) avoided.

Sodium aminosalicylate dihydrate (1993)

Relative molecular mass: corrected.

Related substances: reference solutions (a) and (b) modified; reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015); Identification of impurities section introduced; acceptance criteria now expressed in the quantitative style; limits for impurity B tightened; limit for unspecified impurities and reporting threshold modified in accordance with general monograph *Substances for pharmaceutical use (2034)*, as the maximum daily dose of the substance is above 2 g.

Impurities: section updated.

Sodium chloride (0193)

Identification B: it is considered sufficient to use only reaction (a).

Sodium cromoglicate (0562)

Content: reference to the anhydrous instead of the dried substance, due to the replacement of the loss on drying test.

Identification C: name of reagent *aminopyrazolone R* corrected to *4-aminoantipyrine R*.

Acidity or alkalinity: use of volumetric solutions avoided.

Related substances: in preparation of reference solution (b), volume expressed using fewer significant figures due to qualitative use of this solution; Identification of impurities section added.

Loss on drying: test replaced by semi-micro determination of water.

Sodium lactate solution (1151)

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

Bacterial endotoxins: deleted since the requirement is now covered in the general monograph 2034.

Sodium (*S*)-lactate solution (2033)

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

Bacterial endotoxins: the test is deleted as now covered by the general monograph 2034.

Stearic acid (1474)

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

Functionality-related characteristics: white diamonds have been added showing that this section is only present in the Ph. Eur. text.

Tigecycline (2825)

Water. Use of evaporation technique instead of the classical direct introduction of the probe.

Trypsin (0694)

Assay: Adjustment of preparation of reference solution to account potential trypsin activity differences of future Trypsin BRP batches.

Vancomycin hydrochloride (1058)

Characters: statement on hygroscopicity updated.

Vancomycin B and related substances: pH of solution A and its adjustments to meet the resolution criteria clarified. Volume of reference solution (a) to be prepared adjusted.

Assay: corresponding CRS to be used mentioned in addition to the reference to general chapter *2.7.2*.

Vincamine (1800)

Related substances: modification of preparation of reference solution (b) to improve solubility.

Xylazine hydrochloride for veterinary use (1481)

Identification: test B modified in order to avoid the use of potassium dichromate (REACH).

Related substances: reagent used to describe stationary phase modified.

Zuclopenthixol decanoate (1707)

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

Loss on drying: milder vacuum conditions introduced.