Comments concerning texts published in Issue 12.3

Brief descriptions of the modifications that have been made to new, revised and corrected texts adopted by the European Pharmacopoeia Commission at the June session and published in Issue 12.3 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

2.2.44. Total organic carbon in water for pharmaceutical use

This general chapter has been revised to add method B, which applies to sterilised water for injections (SWFI). The revised text now reflects the changes made to the monograph *Water for injections (0169)*, in which the Oxidisable substances test has been replaced by the Total organic carbon (TOC) test for the control of SWFI.

In addition, the reagents *sucrose R* and *1,4-benzoquinone R* have been replaced by chemical reference substances (CRSs) to streamline the application of the TOC test.

2.7.23. Numeration of CD34/CD45+ cells in haematopoietic products

General: it has been made clear that the general chapter is not restricted to the haematopoietic products that are in the scope of the monograph on *Human haematopoietic stem cells (2323)*.

Use of fluorescent beads: in response to evolving techniques, the requirement for the use of calibrated fluorescent beads in single platform assays has been removed. This update acknowledges that certain methods, such as volumetric flow cytometry, do not require fluorescence reference beads. Consequently, the general chapter now accommodates both methods that use reference beads and newer methods that operate without them.

Selection of parameters: the requirement to use commercially available antibodies has been removed in order to avoid confusion, because in-house methods can be used as described in the general chapter.

Negative control (in Selection of monoclonal antibodies and Sample preparation sections): the text has been updated to state that negative controls are to be used when appropriate.

Number of events analysed: the number of CD45+ events analysed has been modified to reflect current practice.

Collection, transport and storage: this section has been updated to reflect current practice and to remove good practice requirements.

Sample preparation: a recommendation to use a labelling method without washing steps has been added to improve the accuracy and precision of the method.

System settings: the text has been modified to indicate that the threshold setting is dependent on the size of the fluorescent beads; a recommendation to avoid high flow rates has been added.

Editorial modifications have also been made throughout the text for greater clarity.

2.9.42. Dissolution test for lipophilic solid dosage forms

Apparatus: a description and a schematic presentation of the two possible configurations have been added; an option to use suitable heating devices other than a water-bath has been added.

Sampling: the filtration step has been deleted since it is deemed unnecessary for lipophilic dosage forms.

The structure of the text has been updated to align both with current Ph. Eur. style and with the structure of general chapter *2.9.3*. Additional editorial changes have also been made throughout the text.

2.9.43. Apparent dissolution

Apparatus: a description and a schematic presentation of the two possible configurations have been added; an option to use suitable heating devices other than a water-bath has been added; a new figure to display the insert has been added.

Procedure: the aperture size and the wire diameter of the wire cloth screens used have been corrected.

The structure of the text has been updated to align both with current Ph. Eur. style and with the structure of general chapter *2.9.3*. Additional editorial changes have also been made throughout the text.

3.1.17. Cyclo-olefin copolymers

Identification A: The text has been corrected to remove the absorption maxima in the Infrared spectrophotometry identification test, as the given list is not suitable for products on the European market, making compliance impossible. The modified text without the absorption maxima (while retaining comparison with the type sample) has been adopted by the PhEur. Commission and will be published in Issue 12.3.

5.2.5. Management of extraneous agents in immunological veterinary medicinal products

Annex I: avian and equine agents have been added to the lists of extraneous agents to be considered for the risk assessment; the viral agent formerly listed as ‘duck hepatitis virus type 1' has been renamed ‘duck hepatitis A virus (*Avihepatovirus ahepati*)'. Based on these lists, which are non-exhaustive and updated regularly, a list of the extraneous agents that may be present in starting materials of animal or human origin is considered as part of the risk assessment. The lists provided in Annex I do not preclude additional agents from being considered, if necessary.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs.

GENERAL MONOGRAPHS

Methods of preparation of homoeopathic stocks and potentisation (2371)

Methods 1.1.2, 1.5.2 and 4.1.1: to maintain consistency in all sections of the document, the term 'plant' was editorially modified to 'herbal drug'.

Method 5.3: revised to include use of ethanol as preservative for storage and additional homeopathic manufacturing methods currently used by European manufacturers to prepare the first dilution of non-soluble solid starting materials.

VACCINES FOR HUMAN USE

Diphtheria vaccine (adsorbed) (0443)

Absence of toxin and irreversibility of toxoid: the requirement to perform the test for irreversibility of diphtheria toxoid (test after incubation of the diluted toxoid at 37 °C for 6 weeks) routinely on each batch of bulk purified toxoid has been deleted, based on the use of validated detoxification processes that produce an irreversible toxoid for the production of safe diphtheria vaccines. The revised monograph emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified. In the revised monograph, the test for irreversibility is to be carried out during development and when changes are made to the manufacturing process that may impact irreversibility of the toxoid.

Consequently, in the test for absence of toxin performed routinely on each batch of bulk purified toxoid, the incubation period of 6 weeks at 5 °C has also been removed, and the test is performed using a fresh sample.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Eleutherococcus (1419)

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

Identification C: TLC replaced by high-performance thin-layer chromatography (HPTLC) in accordance with general chapter *2.8.25*.

Periploca sepium Bunge: test introduced to avoid toxic adulterations.

Assay:

- ferulic acid reagent replaced by *ferulic acid CRS*;

- *eleutherococcus dry extract for system suitability HRS* introduced for peak identification and system suitability.

MONOGRAPHS

Alteplase concentrated solution (3197)

This monograph has been elaborated in parallel to the revision of the monograph *Alteplase for injection (1170)*, the title of which has been changed to Alteplase powder for injection.

Prior to its revision, monograph *1170* covered requirements for both alteplase active substances and alteplase medicinal products. The requirements for the alteplase active substance have been removed from that monograph and inserted in this new monograph *3197*, and have been updated to reflect current practice. The main changes are listed below:

- a detailed imaged capillary isoelectric focusing procedure has replaced the isoelectric focusing procedure;

- the glycan analysis has been detailed;

- a capillary gel electrophoresis procedure has replaced the SDS-PAGE procedure;

- the Type I/Type II alteplase content analysis by SDS-PAGE has been replaced by a liquid chromatography procedure;

- the peptide mapping, the single chain procedures and the potency assay have been updated.

Alteplase powder for injection (1170)

This monograph is submitted without change marks to improve readability as changes have been made throughout the text.

The monograph has been restructured so that it covers only the alteplase medicinal product. A separate monograph on the active substance (*Alteplase concentrated solution (3197)*) has been elaborated in parallel.

This monograph has undergone a general revision and the analytical procedures described in it have been updated to reflect current practice, in particular:

- the isoelectric focusing procedure has been replaced by a detailed imaged capillary isoelectric focusing procedure;

- the single-chain and monomer content procedures and the potency assay have been updated;

- a capillary gel electrophoresis procedure has been added.

Atomoxetine hydrochloride (2640)

Related substances: concentration of reference solution (c) used for impurity A identification aligned with the test solution (a); reagent used to describe the stationary phase modified to align with the column used during the validation of the analytical procedure.

Beeswax, white (0069)

Characters: general revision of the appearance description; in the solubility section, “warm” added to fatty and essential oils since white beeswax is insoluble in cold fatty and essential

oils; in the relative density section, value restricted to two significant figures since it is approximate and for information only.

Identification: new section with Infrared absorption spectrophotometry test added.

Drop point: Method A (manual method) replaced by Method B (automated method), which is more reproducible, already used by laboratories, has a shorter analysis time and avoids the use of mercury thermometers.

Saponification value: test removed. Instead, test for ester value is performed in which the titrated solution from the acid value test is used as a sample to reduce the amount of reagents used.

Ceresin, paraffins and certain other waxes: temperature at which precipitate is formed increased from 65 °C to 66 °C since the cloud point for beeswaxes with a drop point of 66 °C is typically between 65.5-66 °C.

Glycerol and other polyols: clarification added that the decolorised fuchsin solution must be freshly prepared.

Beeswax, yellow (0070)

Definition: new wording introduced to indicate that the melted comb is filtered to obtain yellow beeswax.

Characters: general revision of the appearance description; in the solubility section, “warm” added to fatty and essential oils since beeswax yellow is insoluble in cold fatty and essential oils; in the relative density section, value estricted to two significant figures since it is approximate and for information only.

Identification: new section with Infrared absorption spectrophotometry test added.

Drop point: Method A (manual method) replaced by Method B (automated method), which is more reproducible, already used by laboratories, has a shorter analysis time and avoids the use of mercury thermometers.

Saponification value: test removed. Instead, test for ester value is performed in which the titrated solution from the acid value test is used as a sample to reduce the amount of reagents used.

Ceresin, paraffins and certain other waxes: temperature at which precipitate is formed increased from 65 °C to 66 °C since the cloud point for beeswaxes with a drop point of 66 °C is typically between 65.5-66 °C.

Glycerol and other polyols: clarification added that the decolorised fuchsin solution must be freshly prepared.

Brivaracetam tablets (3140)

Disintegration: disintegration time widened from 10 min to 15 min for all strengths, based on feedback from a competent authority responsible for the authorisation of generic medicinal products. The new disintegration time remains in line with the general dosage form monograph on *Tablets (0478)*.

Calcium gluconate for injection (0979)

Oxalates: based on feedback from users, the resolution requirement for system suitability has been relaxed.

Chlorhexidine diacetate (0657)

Second identification: in test B (by TLC), derivatisation reagent changed to improve spot detection; test C (reaction (a) of acetates, *2.3.1*) replaced by a test using an indicator to avoid identification by odour.

Chlorhexidine digluconate solution (0658)

Second identification: test C (by melting point after recrystallisation) replaced by a TLC analytical procedure aimed at detecting chlorhexidine moiety in line with the monographs *Chlorhexidine diacetate (0657)* and *Chlorhexidine dihydrochloride (0659)*; test D deleted as considered unsuitable due to the presence of bromine water and unnecessary.

Related substances: following experimental verification, peak-to-valley ratio replaced by resolution criterion between the peaks due to impurities N and B.

Chlorhexidine dihydrochloride (0659)

Second identification: in test B (by TLC), derivatisation reagent changed to improve spot detection.

Cholesterol (0993)

First identification: tests relabelled due to introduction of second identification.

Second identification: subsection added since the substance is used in pharmacies.

Citalopram hydrobromide (2288)

Related substances: in view of new experimental work carried out, correction factor for impurity G deleted as not required when this impurity is quantified at 254 nm versus the active substance in reference solution (a) at 230 nm; detection wavelength for reference solution (a) clarified to avoid confusion.

Clenbuterol hydrochloride (1409)

Related substances: liquid chromatography procedure transformed into a quantitative test where all impurities are quantified with respect to the concentration of clenbuterol hydrochloride; limits updated based on data from manufacturers and the requirements of general monograph *2034* (impurities A, B, C, D, E and F listed as unspecified impurities and limit for unspecified impurities introduced); 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.

Dihydroergocristine mesilate (1416)

Characters: solubility in heptane included.

Identification by IR: preparation as discs deleted.

Related substances: grade of a solvent amended in accordance with the Technical Guide; reagent used to describe stationary phase modified; disregard limit and limits updated based on data from manufacturers; acceptance criterion of 0.2 per cent for ‘unspecified impurities' prescribed due to complex impurity profile of this semisynthetic product (impossible to apply the general policy for impurities described in the general monograph *2034*); resolution criterion updated according to the Technical Guide and based on data from manufacturers;

reference solution (a) introduced for the calculation of impurities; method for identification of impurities introduced, with system suitability criterion ‘the chromatogram shows 4 peaks' deleted as a result.

Fludrocortisone acetate (0767)

Related substances: following further investigation and to avoid degradation, clarification made that the solutions must be stored at 5 °C and used within 42 h; autosampler temperature (set at 5 °C) added.

Fluorouracil (0611)

Impurities F and G: introduction of a new reference solution which contains the substance to be examined and impurities F and G; clarification of the SST requirement.

Related substances: in the preparation of reference solution (g), volume expressed using fewer significant figures due to the qualitative use of this solution; reagent used to describe stationary phase modified.

Hydrocortisone (0335)

Related substances: following additional information from users and in view of available batch and stability data from approved manufacturers, limit for impurity G reduced from 0.4 per cent to 0.3 per cent; grade of water used in the mobile phase amended in accordance with the Technical Guide (2022); editorial change made to the reagent name of the stationary phase.

Insulin aspart (2084)

Peptide mapping: the sulfate buffer solution used to stop the reaction of the protease and for preparation of mobile phases has been revised to remove the requirement to adjust the pH to 2.0, which led to separation of mobile phase B; grades of solvents amended in accordance with the Technical Guide (2022).

Impurities with molecular masses greater than that of insulin aspart: reagent used to describe stationary phase modified.

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

Insulin glargine (2571)

Impurities with molecular masses greater than that of insulin glargine: reagent used to describe stationary phase modified.

Insulin, human (0838)

Peptide mapping: the sulfate buffer solution used to stop the reaction of the protease and for preparation of mobile phases has been revised to remove the requirement to adjust the pH to 2.0, which led to separation of mobile phase B; grades of solvents amended in accordance with the Technical Guide (2022).

Impurities with molecular masses greater than that of insulin: reagent used to describe stationary phase modified.

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

Insulin lispro (2085)

Peptide mapping: the sulfate buffer solution used to stop the reaction of the protease and for preparation of mobile phases has been revised to remove the requirement to adjust the pH to 2.0, which led to separation of mobile phase B; grades of solvents amended in accordance with the Technical Guide (2022).

Impurities with molecular masses greater than that of insulin lispro: reagent used to describe stationary phase modified.

Insulin, porcine (1638)

Peptide mapping: the sulfate buffer solution used to stop the reaction of the protease and for preparation of mobile phases has been revised to remove the requirement to adjust the pH to 2.0, which led to separation of mobile phase B.

Impurities with molecular masses greater than that of insulin: reagent used to describe stationary phase modified.

Insulin preparations, injectable (0854)

Impurities with molecular masses greater than that of insulin: reagent used to describe stationary phase modified.

Macrogolglycerol hydroxystearate (1083)

Identification D: wet chemical reaction replaced by infrared absorption spectrophotometry for increased specificity and to avoid the use of mercuric chloride solution and alkaline potassium tetraiodomercurate solution.

Functionality-related characteristics: a section has been added to introduce characteristics that may be considered critical and useful material attributes when macrogolglycerol hydroxystearate is used as emulsifier or solubiliser in liquid dosage forms (parenteral and non-parenteral) and in semi-solid preparations. The three characteristics added are molecular mass distribution and cross-references to hydroxyl and saponification values.

Macrogolglycerol ricinoleate (1082)

Identification D: wet chemical reaction replaced by infrared absorption spectrophotometry for increased specificity and to avoid the use of mercuric chloride solution and alkaline potassium tetraiodomercurate solution.

Solution S: editorial change; solution removed, and preparation integrated into appearance since it only applies to appearance.

Functionality-related characteristics: a section has been added to introduce characteristics that may be considered critical and useful material attributes when macrogolglycerol ricinoleate is used as emulsifier or solubiliser in liquid dosage forms (parenteral and non-parenteral) and in semi-solid preparations. The 3 characteristics added are molecular mass distribution and cross-references to hydroxyl and saponification values.

Malic acid (2080)

Identification by IR: reference spectrum replaced with a reference substance.

Solution S: sample mass expressed using fewer significant figures.

Related substances: alignment of the monograph with the L-Malic acid monograph (*3143*) published in Pharmeuropa 36.2; concentration of test solution increased from 1 mg/mL to 20 mg/mL; change to quantitative style; limits updated based on manufacturer's data and requirements of the general monograph *Substances for pharmaceutical use (2034)*; limit for impurity C included.

Impurities: impurity C introduced.

Oxygen (0417)

Definition: this monograph covers oxygen produced via cryogenic distillation. This information has been moved from the Production section to the Definition section.

Characters: the solubility statement has been deleted as this property was taken from the literature and cannot easily be verified.

Production: the tests given in the Production section have been moved to the Tests section, to replace the indicator tube tests. The indicator tubes were originally introduced to determine the level of the impurities in the gas at the terminal outlets of the medical gas pipeline system (MGPS). As the scope of the monograph only defines the quality of the gas being delivered to the MGPS (and not at the terminal outlet) and the indicator tube test methods could not be validated, the latter have been removed. The monograph does not exclude the performance of additional tests on-site using semi-quantitative methods such as indicator tubes, in the form of spot checks by the healthcare facility to verify the quality of the gas at the terminal outlet of the medical gas pipeline; such practice would be outside the scope of the Ph. Eur.

Oxygen (93 per cent) (2455)

Definition: this monograph covers oxygen produced via a single-stage adsorption plant. This information has been moved from the Production section to the Definition section.

Production: the tests given in the Production section have been moved to the Tests section, to replace the indicator tube tests. The indicator tubes were originally introduced to determine the level of the impurities in the gas at the terminal outlets of the medical gas pipeline system (MGPS). As the scope of the monograph only defines the quality of the gas being delivered to the MGPS (and not at the terminal outlet) and the indicator tube test methods could not be validated, the latter have been removed. The monograph does not exclude the performance of additional tests on-site using semi-quantitative methods such as indicator tubes, in the form of spot checks by the healthcare facility to verify the quality of the gas at the terminal outlet of the medical gas pipeline; such practice would be outside the scope of the Ph. Eur.

The required frequency of the analytical procedures used for the assay and the tests for carbon dioxide, carbon monoxide and water has been aligned with the monograph on Oxygen (98 per cent).

Carbon dioxide: the composition of reference gas (b) used in the test for carbon dioxide has been modified to simplify the relevant test method and to allow the same gases to be used for the calibration of the impurities in the monographs on *Oxygen (98 per cent) (3098)*, *Oxygen (93 per cent) (2455)* and *Oxygen (0417)*.

Other impurities: section requiring the performance of a risk assessment has been added.

Storage: a section has been added to align with the monograph on *Oxygen (98 per cent) (3098)*.

Labelling: a section has been added to align with the monograph on *Oxygen (98 per cent) (3098)*.

Oxygen (98 per cent) (3098)

Carbon dioxide and Carbon monoxide: the composition of the reference gases has been modified to simplify relevant test methods and to allow the same gases to be used for the monographs on *Oxygen (98 per cent) (3098)*, *Oxygen (93 per cent) (2455)* and *Oxygen (0417*).

Pergolide mesilate (1555)

Identification by IR: preparation as discs deleted.

Related substances: liquid chromatography procedure transformed into a quantitative test where all impurities are quantified with respect to the concentration of pergolide mesilate; reporting threshold and limits updated based on data from manufacturers and the requirements of general monograph *2034*; grade of water amended in accordance with the Technical Guide; reagent used to describe stationary phase modified.

Assay: grade of water amended in accordance with the Technical Guide; reagent used to describe stationary phase modified; requirement for symmetry factor deleted since covered by general chapter *2.2.46* and based on data from manufacturers.

Pilocarpine hydrochloride (0633)

Characters: solubility in heptane included; statement "It is sensitive to light" added in accordance with the Technical guide and to align with the corresponding statement in the storage section and the monograph on *Pilocarpine nitrate (0104)*.

Related substances: liquid chromatography procedure transformed into a quantitative test where all impurities are quantified with respect to the concentration of pilocarpine hydrochloride; reporting threshold and limits updated based on data from one manufacturer and the requirements of general monograph *2034* (impurity B listed as unspecified impurity and limit for unspecified impurities introduced); grades of solvents amended in accordance with the Technical Guide; in the preparation of reference solution (b), volume/mass expressed using fewer significant figures due to the qualitative use of this solution; reference solution (c) deleted since impurity B is no longer specified; concentration of reference solution (a) with respect to test solution decreased from 0.5 per cent to 0.1 per cent; reagent used to describe stationary phase updated.

Pilocarpine nitrate (0104)

Definition: lower limit for assay tightened from 98.5 per cent to 99.0 per cent in accordance with the Technical guide, considering assay determination by non-aqueous titration with the recommended content limits of ± 1.0 per cent.

Characters: solubility in heptane included.

Related substances: liquid chromatography procedure transformed into a quantitative test where all impurities are quantified with respect to the concentration of pilocarpine nitrate; reporting threshold and limits updated based on data from manufacturers and the requirements of general monograph *2034* (impurity B listed as unspecified impurity and limit for unspecified impurities introduced); grades of solvents amended in accordance with the Technical Guide; in the preparation of reference solution (b), volume/mass expressed using

fewer significant figures due to the qualitative use of this solution; reference solution (c) deleted since impurity B is no longer specified; concentration of reference solution (a) with respect to test solution decreased from 0.5 per cent to 0.1 per cent; reagent used to describe stationary phase updated.

Pregabalin (2777)

Enantiomeric purity: 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: procedures for polar impurities eluting before pregabalin and non-polar impurities eluting after pregabalin replaced by a single gradient high-performance liquid chromatography (HPLC) procedure, allowing the control of all listed impurities; introduction of additional impurities.

Assay: new HPLC procedure used for the Related substances test to be used for the assay as well.

Impurities: transparency list updated to include new impurities.

Ropinirole hydrochloride (2604)

Related substances: introduction of a more powerful UHPLC test procedure, allowing better separation of impurities E and H; addition of new impurity I; introduction of a peak-to-valley ratio (impurity A:ropinirole); impurity C considered as specified impurity with correction factor of 0.5 and limit of 0.10 per cent.

Assay: isocratic elution procedure based on the one used for the related substances test; addition of system suitability test (peak-to-valley ratio of impurity A:ropinirole).

Water: accuracy of sample size decreased in accordance with the Technical Guide (8th Ed.).

Rosuvastatin calcium tablets (3008)

Related substances: following further investigation and to avoid degradation, clarification made that the solutions must be stored at 5 °C and used within 45 h; autosampler temperature (set at 5 °C) added.

Sodium hyaluronate (1472)

Loss on drying: the test has been revised to remove the use of diphosphorus pentoxide and to prescribe drying in an oven without any desiccant. This revision is a consequence of the revision of general chapter *2.2.32. Loss on drying* in Supplement 9.8 as a part of the initiative to remove or replace diphosphorus pentoxide in Ph. Eur. texts.

Chlorides: a revised method with improved performance has been introduced.

Tryptophan (1272)

Appearance of solution: grades of solvents amended in accordance with the Technical Guide (2022).

Ninhydrin-positive substances: accuracy of volumes in reference solution (d) decreased in accordance with the Technical Guide (2022).

Impurity A and other related substances: *N*-acetyltryptophan is used as a retention time indicator for calculating the sum of impurities eluting before or after it and is not an impurity of tryptophan; test solution (b) deleted; in the resolution section, information about the adjustment of conditions deleted since values much higher than 8.0 observed; system suitability criterion linked to peak eluting at retention time of *N*-acetyltryptophan deleted; in the disregard limit section, "disregard any peak due to *N*-acetyltryptophan" deleted; factors used for the sums of impurities corrected; stationary phase reagent changed; suitable HPLC column tradename added as a footnote; accuracy of sample size increased in accordance with the Technical Guide (2022) (test solution); grades of solvents amended in accordance with the Technical Guide (2022).

Vitamin A concentrate (oily form), synthetic (0219)

Assay Method B: calculation formula rectified to account for the total volume to which both the preparation to be examined and *retinol acetate CRS* are diluted to give 100 IU/mL. The same change applied to monographs *0218* and *0220*.

Vitamin A concentrate (powder form), synthetic (0218)

Assay: calculation formula rectified to account for the total volume to which both the preparation to be examined and *retinol acetate CRS* are diluted to give 100 IU/mL. The same change applied to monographs *0219* and *0220*.

Vitamin A concentrate (solubilisate/emulsion), synthetic (0220)

Assay: calculation formula rectified to account for the total volume to which both the preparation to be examined and *retinol acetate CRS* are diluted to give 100 IU/mL. The same change applied to monographs *0218* and *0219*.

Water for injections (0169)

This monograph has been revised to replace the Oxidisable substances test by the Total organic carbon (TOC) test in the section Sterilised water for injections (SWFI).

The TOC test is known to be a more robust and state-of-the-art method than the colorimetric oxidisable substances method. This revision is a step towards the international harmonisation of the requirements for SWFI, an important excipient widely used by pharmaceutical manufacturers.

In addition, the following modifications have been made for Water for injections in bulk.

- *Total organic carbon (TOC)*: a reference to method A described in general chapter *2.2.44. Total organic carbon in water for pharmaceutical use* has been added; the limit has been corrected from 0.5 mg/L to 0.50 mg/L, based on the concentration of the standard solution used in general chapter *2.2.44*.

- *Conductivity*: the accuracy has been corrected from "within 3 per cent of the measured conductivity plus 0.1 $\mu S \cdot cm^{-1}$" to "within 3 per cent of the expected conductivity value for each reference solution plus 0.1 $\mu S \cdot cm^{-1}$" under System calibration (conductivity cell and conductometer).

Water, purified (0008)

This monograph has been revised following the revision of general chapter *2.2.44. Total organic carbon in water for pharmaceutical use*.

The following modifications have been made for Purified water in bulk.

- *Total organic carbon (TOC)*: a reference to method A described in general chapter *2.2.44* has been added; the limit has been corrected from 0.5 mg/L to 0.50 mg/L, based on the concentration of the standard solution used in general chapter *2.2.44*.

- *Conductivity*: the accuracy has been corrected from “within 3 per cent of the measured conductivity plus 0.1 µS·cm^{-1}” to “within 3 per cent of the expected conductivity value for each reference solution plus 0.1 µS·cm^{-1}” under System calibration (conductivity cell and conductometer).

Ziprasidone hydrochloride monohydrate (2421)

Related substances: preparation of test solution (a) and reference solution (a) modified in view of additional experimental results and to ensure solubilisation of the substances.

Assay: preparation of test and reference solutions modified in view of additional experimental results and to ensure solubilisation of the substances.

Ziprasidone mesilate trihydrate (2649)

Related substances: preparation of reference solution (a) updated to ensure complete solubilisation of the CRS.