

## Comments concerning texts published in Supplement 11.3

*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 Supplement 11.3 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 online version of the European Pharmacopoeia are now indicated by change marks in the form of triangles. For reasons of readability, these triangles are not shown in the print version, but users will still be able to determine if a text has been corrected or revised from the version date indicated above the title of the monograph and, if applicable, by 'corrected X.X', indicating publication of a corrected version in Supplement X.X.*

### GENERAL CHAPTERS

#### 2.2.35. Osmolality

**Calibration and adjustment.** The requirements have been clarified and the zero point determination is now avoided.

**Accuracy check.** This section has been included to provide additional detail and clarify previous requirements. The acceptance criterion has been revised to account for the extension of the osmolality reference solutions to values up to 4000 mosmol/kg.

**Reference solutions.** This section has been added to provide more guidance on the in-house preparation of osmolality reference solutions using sodium chloride.

**Table 2.2.35.-1.** The preparation of the historical reference solutions in the range 100-700 mosmol/kg has been revised according to a new assessment of the scientific data available. The table has also been extended to include osmolality values up to 4000 mosmol/kg.

**Measurement.** The description has been rendered more general.

#### 2.2.46. Chromatographic separation techniques

**Signal-to-noise ratio (S/N):** the calculation of the S/N ratio as prescribed in supplements 6.4 to 10.8, i.e. a calculation on a window of at least 5 times the peak width at half height, has been reinstated instead of 20 times (as prescribed in the 11<sup>th</sup> Ed.). The chromatograms in Figures 2.2.46.-6 and 2.2.46.-7 have been amended accordingly. See also [News](#).

**System sensitivity.** The explanation (local requirement) on which solution to use to calculate the S/N ratio has been corrected since the S/N ratio is based on peak height and peak width at half-height, not on peak area. For more clarity, "extrapolate the signal-to-noise ratio" is now stated and the whole recommendation is simplified.

### 2.6.16. Tests for extraneous agents in viral vaccines for human use

**Table 2.6.16.-1.** The table has been updated to make it clearer that a haemadsorbing test is performed not only on control cells, but also on virus seed lots and virus harvests (as part of the *Test for extraneous agents in cell cultures*).

In footnote (6), the wording has been revised to reflect that “eggs” are already covered by the term “primary avian tissues”.

Footnote (9) has been added to clarify that the *Test for mycobacteria* and *Test for extraneous agents in cell cultures* on viral harvests are not applicable to inactivated viral vaccines.

A sentence has been added to stress that the table and the method descriptions are to be read together as they contain complementary information.

**Avian viruses.** The text has been clarified to reflect that haemagglutination testing should only be performed on the allantoic fluids of eggs containing live embryos (i.e. no haemagglutination testing on yolk sac fluids).

**Test for extraneous agents in cell cultures.** To facilitate reading, all information related to the *Test for extraneous agents in cell cultures* on virus seed lots, virus harvests and control cells/eggs has been gathered under this section (previously, the section only described the test applied to virus seed lots and virus harvests, with the operating conditions for control cells/eggs given elsewhere).

Human and simian cell cultures are inoculated in the test. The wording has been revised to clarify that only the simian cell cultures (not the human cell cultures) should be continuous.

Prior neutralisation of the vaccine virus applies to both virus seed lots and virus harvests. The text has been amended accordingly.

The text foresees that a haemadsorbing test be carried out on virus seed lots, virus harvests, control cells and supernatant fluids of control cells. The new wording clarifies that the operating conditions of the haemadsorbing test are those described in the section on *haemadsorbing viruses*.

**Insect viruses.** It has been clarified that the operating conditions of the haemadsorbing test are those described in the section on *haemadsorbing viruses*.

**Tests on control cells.** It has been clarified that the operating conditions of the haemadsorbing test are those described in the section on *haemadsorbing viruses*. The paragraph related to the *Test for extraneous agents in cell cultures* on the supernatant fluids of control cells has been moved to the corresponding section. As a result, the section has been renamed “*Examination of control cells*”.

**Haemadsorbing viruses.** The paragraph specific to control cells has been moved to the section on *Examination of control cells*. It was clarified in the acceptance criterion that no evidence of haemadsorbing or haemagglutinating agents should be found.

**Tests on control eggs.** Editorial improvements have been introduced to make it clear that two distinct tests for haemagglutinating agents are carried out: 1) a direct test on the allantoic fluid of each control egg; 2) an indirect test on pooled amniotic fluids from control eggs inoculated into SPF eggs. The paragraph related to the *Test for extraneous agents in cell cultures* on pooled amniotic fluids from control eggs has been moved to the corresponding section. As a result, the section has been renamed *Tests for haemagglutinating agents on control eggs*.

**Test for avian leucosis viruses.** The scope of the section has been extended to cover virus seed lots, in addition to control cells/eggs.

The description of the test has been revised to integrate general considerations and specific considerations for seed lots that were previously provided in general chapter 2.6.24. *Avian viral vaccines: tests for extraneous agents in seed lots* (chapter now deleted from the Ph. Eur.). The elements imported from chapter 2.6.24 include: volume to be inoculated (seed lots), positive controls and cycles of thawing and freezing.

The number of passages has also been changed from 5 to at least 4, based on published data.

### 2.7.28. Colony-forming cell assay for human haematopoietic progenitor cells

General chapter updated to:

- include automated systems;
- improve the standardisation of the analytical procedure (e.g. to standardise using the number of plated cells and the numbers of CD34/CD45+ cells seeded by plate) ;
- include a more detailed description of validation requirements;
- address the possibility to use serum-free medium and recombinant growth factors;
- include a clarification on the definition of colony forming cells and their functional capacity.

The general chapter is provided without markup changes to improve readability as editorial modifications have been made throughout the text.

### 2.7.29. Nucleated cell count and viability

The revised chapter includes new automated technologies for cell enumeration.

The main modifications to the chapter are:

- the plan of the chapter: manual and automated methods are separated into two distinct sections;
- a sample preparation and test conditions section is included to improve the standardisation of the method;
- a table summarises information on commonly used dyes;
- image cytometry technologies are described;
- a table summarises the main characteristics of flow cytometry and image cytometry, which are the most commonly used techniques for automated counting and viability;
- a validation section is included, it corresponds to accepted scientific practice and current recommendations on analytical validation such as ICH Q2 guideline(R1).

The general chapter is provided without markup changes to improve readability as editorial modifications have been made throughout the text.

### 2.9.7. Friability of uncoated tablets

The following sections were revised:

- Equipment: uniform presentation of the dimensional requirements for the apparatus.

- Procedure: clarification of the test criteria and other minor wording changes for clarity (e.g. specification in case of effervescent and chewable tablets).

### 5.12. Reference standards

English version corrected. In section 4-1, reinsertion of the first paragraph on test programme that was omitted in the 11<sup>th</sup> Edition.

### 5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs published in Supplement 11.1.

## GENERAL MONOGRAPHS

### Pharmaceutical preparations (2619)

**Production:** addition of a paragraph explaining the Ph. Eur. approach for *N*-nitrosamine impurities. This approach has been defined based on the feedback from Heads of Medicines Agencies & European Medicines Agency groups (Joint CHMP/CVMP Quality Working Party, Biologics Working Party, Committee for Veterinary Medicinal Products, Herbal Medicinal Products Committee, Homeopathic Medicinal Products Working Group) as well as from National Competent Authorities of non-EU Ph. Eur. member states.

**Glossary:** reference to “authorised pharmaceutical preparation” as a synonym of “licensed pharmaceutical preparation” deleted to ensure that the definition also covers medicinal products released onto the market via processes other than marketing authorisation.

**Additional information of interest:** CHMP\* opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 regarding the detection, management and prevention of presence of *N*-nitrosamines in medicinal products for human use (see assessment report published on 25 June 2020\*\*) and CHMP\* decision to apply these recommendations to “sartans medicinal products” (see news published on 13 November 2020\*\*\*).

\*CHMP: Committee for Human Medicinal Products of the European Medicines Agency

\*\*[https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf)

\*\*\*<https://www.ema.europa.eu/en/news/nitrosamines-ema-aligns-recommendations-sartans-those-other-medicines>

### Substances for pharmaceutical use (2034)

**Production:** addition of a paragraph explaining the Ph. Eur. approach for *N*-nitrosamines impurities. This approach has been defined based on the feedback from Heads of Medicines Agencies & European Medicines Agency groups (Joint CHMP/CVMP Quality Working Party, Biologics Working Party, Committee for Veterinary Medicinal Products, Herbal Medicinal Products Committee, Homeopathic Medicinal Products Working Group) as well as from National Competent Authorities of non-EU Ph. Eur. member states.

**Additional information of interest:** CHMP\* opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 regarding the detection, management and prevention of presence of

*N*-nitrosamines in medicinal products for human use (see assessment report published on 25 June 2020\*\*) and CHMP\* decision to apply these recommendations to “sartans medicinal products” (see news published on 13 November 2020\*\*\*).

\*CHMP: Committee for Human Medicinal Products of the European Medicines Agency

\*\*[https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf)

\*\*\*<https://www.ema.europa.eu/en/news/nitrosamines-ema-aligns-recommendations-sartans-those-other-medicines>

## VACCINES FOR HUMAN USE

### Influenza vaccine (live, nasal) (2772)

**Virus seed lots.** Test for avian leucosis viruses deleted. A test for avian leucosis viruses on virus seed lots is described in the revised general chapter 2.6.16. *Tests for extraneous agents in viral vaccines for human use* published in the same Supplement. As a result, the monograph requirement for virus seed lots to comply with chapter 2.6.16 already covers the test for avian leucosis viruses, making further references to the test redundant.

**Propagation and harvest.** A reference to the revised chapter 2.6.16 has been included in the test for avian leucosis viruses. The test for avian leucosis viruses of chapter 2.6.16 may be used to verify the absence of avian leucosis viruses in virus harvests.

### Yellow fever vaccine (live) (0537)

**Avian leucosis viruses.** References to the test for avian leucosis viruses moved to the tests for Extraneous agents for master and working seed lots. A test for avian leucosis viruses on virus seed lots is described in the revised general chapter 2.6.16. *Tests for extraneous agents in viral vaccines for human use* published in the same Supplement.

## RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

### Alovudine (<sup>18</sup>F) injection (2460)

**Impurity B - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph. Reagent used to describe stationary phase modified.

### Fludeoxyglucose (<sup>18</sup>F) injection (1325)

**2-Fluoro-2-deoxy-D-glucose and impurity A:** reagent used to describe stationary phase modified.

**Impurity C - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph. Reagent used to describe stationary phase modified.

### Fluorocholine (<sup>18</sup>F) injection (2793)

**Identification C:** wording adapted to take account of the revised test for [<sup>18</sup>F]fluorocholine, see below.

**Impurity D (tetrabutylammonium):** LC test replaced by the test given in general method (2.4.33), which is a faster and more reliable TLC procedure.

**Fluorocholine and impurity F:** introduction of a new test, ensuring the control of a new impurity, impurity F (bromocholine).

**[<sup>18</sup>F]Fluorocholine:** replacement of the test by cross reference to the new LC test given under "Fluorocholine and impurity F".

### Fluorodopa (<sup>18</sup>F) (prepared by nucleophilic substitution) injection (2481)

**Impurity D - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Fluoromisonidazole (<sup>18</sup>F) injection (2459)

**Impurity B - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Technetium (<sup>99m</sup>Tc) sestamibi injection (1926)

**Definition:** the information related to the production of the preparation has been transferred to the newly created Production section.

**Production:** a section was created requiring that *Sodium pertechnetate (<sup>99m</sup>Tc) injection (fission) (0124)*, *Sodium pertechnetate (<sup>99m</sup>Tc) injection (non-fission) (0283)* or *Sodium pertechnetate (<sup>99m</sup>Tc) injection (accelerator-produced) (2981)* and *Copper tetramibi tetrafluoroborate for radiopharmaceutical preparations (2547)* be used to prepare Technetium (<sup>99m</sup>Tc) sestamibi injection.

**Radiochemical impurities determined by LC:** procedure and specifications updated to reflect the current quality of technetium (<sup>99m</sup>Tc) sestamibi injection.

## HERBAL DRUGS AND HERBAL DRUGS PREPARATION

### Agnus castus fruit (2147)

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

**Other species of Vitex, in particular Vitex negundo L.:** test deleted since the possibility of adulteration with other species of Vitex, including *Vitex negundo* L., is considered very low; in addition, the diameter of the fruit does not appear to be a distinguishing feature between *Vitex*

*agnus-castus* L. and *Vitex negundo* L., or between *Vitex agnus-castus* L. and other relevant species of *Vitex*.

### Black horehound (1858)

**Identification C:** TLC replaced by HPTLC in accordance with general chapter 2.8.25; description revised to cover variety of samples on the market.

**Assay:** editorially modified in accordance with current style.

### Bogbean leaf (1605)

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

### Cola (1504)

**Definition:** statement on varieties deleted since this is considered redundant.

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

### Guarana (2669)

**Identification C:** fast blue B salt as derivatisation reagent replaced by anisaldehyde due to toxicity; HPTLC in accordance with general chapter 2.8.25 introduced.

**Assay:** run time reduced to twice the retention time of caffeine since this is considered sufficient for the purpose of the procedure.

### Ispaghula husk (1334)

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

### Mate leaf (2678)

**Identification C:** to improve reproducibility, TLC replaced by HPTLC in accordance with general chapter 2.8.25.

### Milk thistle dry extract, refined and standardised (2071)

**Identification:** drying and detection steps updated; colour added for the lowest zone described in the plate for the test solution.

**Assay:**

- it has been confirmed by mass spectrometry that the peak eluting in the tail of the peak due to silibinin B is not due to dihydrosilibinin B, but corresponds to one or more silibinin diastereoisomers. Therefore, the peak identification has been updated;
- last gradient step deleted in accordance with current policy about not including in monographs the return to initial conditions; statement on adjusting the gradient if necessary in the retention time section deleted since this is covered by general chapter 2.2.46; second system suitability criterion deleted since it lacks discriminatory power.

### Milk thistle fruit (1860)

**Definition:** synonym *Carduus marianus* L. added.

**Identification B:** illustration of powdered herbal drug introduced and its legend integrated into text of identification B; drying step, detection step and general statement on results, of identification C, updated.

**Assay:**

- it has been confirmed by mass spectrometry that the peak eluting in the tail of the peak due to silibinin B is not due to dihydrosilibinin B, but corresponds to one or more silibinin diastereoisomers. Therefore, the peak identification has been updated;
- last gradient step deleted in accordance with current policy about not including in monographs the return to initial conditions; statement on adjusting the gradient if necessary in the retention time section deleted since this is covered by general chapter 2.2.46; second system suitability criterion deleted since it lacks discriminatory power.

### Oak bark (1887)

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

### Pelargonium root (2264)

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

### Psyllium seed (0858)

**Definition:** *Plantago psyllium* L. correctly listed as synonym of *Plantago indica* L. rather than of *Plantago afra* L.; number of synonyms listed reduced to one in order to keep the most commonly used.

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

**Foreign matter:** names of species deleted since these do not serve any purpose in the interpretation of the corresponding acceptance criteria and may imply the need to identify the species of non-compliant seeds.

### Tormentil (1478)

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

## HOMOEOPATHIC PREPARATIONS

### Calcium iodatum for homoeopathic preparations (2144)

**Identification A:** modified in order to avoid the use of chloroform.

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



## Nux-vomica for homoeopathic preparations (2514)

**Definition.** The lower limit of the sum of the contents of brucine and strychnine of nux-vomica seeds has been slightly lowered (i.e. from “1.50 per cent” to “1.30 per cent”) and the lower limit for the sum of the contents of brucine and strychnine of the mother tinctures produced with these seeds has also been slightly lowered (i.e. from “0.15 per cent *m/m*” to “0.13 per cent *m/m*”).

# MONOGRAPHS

## Amikacin (1289)

**Assay - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

## Ampicillin sodium (0578)

**Production:** the control of *N,N*-dimethylaniline has been moved from the Tests section to the Production section in order to be aligned with the approach adopted for other antibiotics monographs.

**Related substances:** the retention time of ampicillin and the relative retention of cefradine have been introduced. The grades of solvents have been amended in accordance with the Technical Guide (2015).

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

**Methylene chloride:** the test has been deleted to avoid the use of a reagent proscribed under the REACH regulation (ethylene chloride). The control of residual solvents is covered by the general monograph *Substances for pharmaceutical use (2034)* and the general chapter 5.4. *Residual solvents*.

**Bacterial endotoxins:** the test has been deleted in accordance with the Ph. Eur. policy adopted in February 2015 (see Pharmeuropa online, Technical information).

## Atracurium besilate (1970)

**Characters:** information about the hygroscopicity of the substance has been updated in view of recent data from manufacturers of approved medicinal products.

**Related substances:** additional statement introduced to alert users on the need to prepare the solutions immediately before use, following investigation on the stability of the solutions.

## Benzylpenicillin (benzathine) tetrahydrate (0373)

**Assay - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Bismuth subcarbonate (0012)

**Formulae, mass and CAS number:** graphic formula, molecular formula, relative molecular mass and CAS number have been added.

**Definition:** chemical name has been added.

**Arsenic, Copper, Lead, Silver:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see [Press release](#)), the tests have been deleted.

### Bismuth subgallate (1493)

**Definition:** chemical name has been added.

**Solution S:** following the deletion of the tests for copper, lead and silver, this solution is no longer needed and has been deleted.

**Copper, Lead, Silver:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see [Press release](#)), the tests have been deleted.

### Bismuth subnitrate, heavy (1494)

**Definition:** chemical name has been added.

**Solution S1:** since solution S2 is no longer needed in the Tests section, solution S1 has been renamed solution S.

**Solution S2:** following the deletion of the tests for copper, lead and silver, the preparation of this solution is now described under Identification D since it is only used for this test.

**Copper, Lead, Silver:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see [Press release](#)), the tests have been deleted.

### Bismuth subsalicylate (1495)

**Formulae:** graphic formula has been added.

**Definition:** chemical name has been added.

**Solution S:** following the deletion of the tests for copper, lead and silver, this solution is no longer needed and has been deleted.

**Copper, Lead, Silver:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see [Press release](#)), the tests have been deleted.

### Cefaclor (0986)

**Related substances.** Grade of one of the solvents amended in accordance with the Technical Guide (2022).

**Assay - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Cholecalciferol (0072)

**Related substances:** replacement of hexane (class 2 solvent) by heptane (class 3 solvent); change to quantitative style; increase of the volume of reference solution (a), and of the test solution accordingly, to allow its use for both assay and preparation of reference solution (c).

**Impurities:** addition of an unspecified impurity (F).

### Clarithromycin (1651)

**Related substances - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Dabigatran etexilate mesilate (3095)

**Related substances:** the limit for total impurities was tightened to 1.0 per cent after the public consultation in Pharmeuropa in accordance with information shared by manufacturers/ MAHs in Europe.

### Donepezil hydrochloride (2582)

**Graphic formula, molecular formula, Definition and Characters:** updated, since the revised monograph covers the anhydrous and monohydrate forms of donepezil hydrochloride; statements on hygroscopicity and polymorphism added.

**Identification:** recrystallisation step added in test A; test B deleted since the revised monograph covers the anhydrous and monohydrate forms of donepezil hydrochloride.

**Water:** specification widened to cover anhydrous non-hygroscopic, anhydrous hygroscopic and monohydrate forms of the API. Water contents of up to 6.1 per cent and specifications of maximum 7.0 per cent have been reported for the anhydrous hygroscopic form. Consequently, the ranges of water content in anhydrous and monohydrate forms of donepezil hydrochloride may overlap because the hygroscopic form of anhydrous donepezil hydrochloride can absorb water up to the same level as the total water content found in donepezil hydrochloride monohydrate.

**Impurities:** stereochemistry of impurity C updated; identity of impurity G corrected and now expressed as impurity H.

### Fluocortolone pivalate (1212)

**Related substances:** in view of recent batch data from a manufacturer of an approved product, impurity A becomes specified at 0.3 per cent and needs to be identified with a new CRS.

### Halofantrine hydrochloride (1979)

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

**Related substances:** the limit for unspecified impurities has been introduced in line with requirements of the general monograph *Substances for pharmaceutical use (2034)*. All impurities are now covered by the explicit criterion for unspecified impurities. Editorial change in the reagent name of the stationary phase.

**Impurities:** the transparency list has been updated.

### Human coagulation factor IX (1223)

**Labelling section:** the text that had been erroneously deleted in the Ph. Eur. 11<sup>th</sup> Edition has been reinstated.

### Infliximab concentrated solution (2928)

The chemical structure of infliximab and the chromatogram for glycan analysis of infliximab (Figure 2928.-1), which were erroneously deleted from the print version of Ph. Eur. Supplement 11.1, have been reinstated.

### Iodixanol (2215)

**Impurities E and H:** the description of reference solution (c) has been changed due to a change in the preparation of *iodixanol impurity E CRS*.

### Isoniazid (0146)

The chemical structures of isoniazid and impurities A, B, C, D and E, which were erroneously deleted from the print version of Ph. Eur. Supplement 11.1, have been reinstated.

### Isopropyl myristate (0725)

**Definition:** upper content limit added in accordance with the Technical Guide for the Elaboration of Monographs 7<sup>th</sup> Edition (2015) and to reflect the current quality of substances in approved medicinal products on the European market.

**CAS number:** added.

### Lactose (1061)

The chemical structure of lactose, which was erroneously deleted from the print version of Ph. Eur. Supplement 11.1, has been reinstated.

### Lactose monohydrate (0187)

The chemical structure of lactose monohydrate, which was erroneously deleted from the print version of Ph. Eur. Supplement 11.1, has been reinstated.

### Latanoprost (2230)

**Related substances:** due to the immiscibility of the active substance with heptane and in order to improve the repeatability of results, heptane has been replaced by the mobile phase as the solvent used for the preparation of reference solution (b).

### Letrozole (2334)

**Assay - symmetry factor:** default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

**Water:** the mention of a validated iodiosulfurous reagent is unnecessary; this information is contained in the Knowledge database.

### Levomepromazine hydrochloride (0505)

The chemical structures of levomepromazine hydrochloride and impurities A, B, C, D and E, which were erroneously deleted from the print version of Ph. Eur. Supplement 11.1, have been reinstated.

### Mepyramine maleate (0278)

**Related substances:** impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market.

### Neostigmine bromide (0046)

**Identification:** reaction (b) of bromides has been deleted from test D as it requires the use of lead dioxide R, a REACH (annex XIV) reagent. Test D now therefore refers to reaction (a) of bromides only.

### Omega-3-acid triglycerides (1352)

**Definition:** molecular distillation added as an example for the purification of the starting materials.

### Pimozide (1254)

**Related substances:** impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; system suitability criterion amended.

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

### Potassium acetate (1139)

**Identification A:** identification of acetates by odour (reaction a) has been replaced by a more suitable reaction (b).

### Rabeprazole sodium (2868)

**Loss on drying:** detailed conditions now described.

### Raloxifene hydrochloride (2375)

**Related substances/Assay - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Raltegravir potassium chewable tablets (2939)

**Title:** revised to bring it in line with the policy for the development of monographs on medicinal products containing chemically defined active substance salts or base/acids.

**Related substances:** correction factor for impurity C deleted and limit decreased accordingly from 0.3 to 0.2 per cent.

### Raltegravir potassium tablets (2938)

**Title:** revised to bring it in line with the policy for the development of monographs on medicinal products containing chemically defined active substance salts or base/acids.

**Related substances:** correction factor for impurity C deleted and limit decreased accordingly from 0.5 to 0.3 per cent.

### Salbutamol (0529)

**Characters:** solubility in methylene chloride added.

**Identification:** second identification series deleted since substance not used in pharmacies.

**Solution S:** section deleted since it is rendered obsolete by the proposed changes.

**Optical rotation:** test deleted since it does not provide a critical assessment of impurities.

**Related substances:** new LC method introduced that also covers impurity J and 7 new impurities; limits updated.

**Impurity J:** test deleted since impurity J is now covered by related substances test.

**Impurities:** section updated.

### Salbutamol sulfate (0687)

**Characters:** statement on polymorphism deleted, since no evidence of the existence of different crystalline forms is reported by current manufacturers.

**First identification:** tests relabeled due to changes in the second identification; recrystallisation step in former test B (now A) deleted.

**Second identification:** former tests A and D deleted because the remaining tests (now B and C), i.e. TLC and reaction (a) of sulfates are considered sufficient.

**Solution S:** volume and mass are expressed using fewer significant figures.

**Optical rotation:** test deleted since it does not provide a critical assessment of impurities.

**Related substances:** LC method optimised, now covering 3 additional impurities; limits updated.

**Impurities:** section updated.

### Sevoflurane (2269)

The chemical structures of sevoflurane and impurities A, B and C, which were erroneously deleted from the print version of Ph. Eur. Supplement 11.1, have been reinstated.

### Sitagliptin tablets (2927)

**Identification C:** editorial modification.

**Related substances:** preparation of reference solution (c) modified to obtain the same final concentration when using a tablet.

### Sotalol hydrochloride (2004)

**Optical rotation:** test deleted as it is considered obsolete given the other tests for purity in the text.

**Related substances:** test optimised; specifications updated based on batch data provided by manufacturers; introduction of a limit for unspecified impurities; acceptance criteria expressed in the quantitative style.

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

### Soya-bean oil, refined (1473)

**Composition of fatty acids.** The limits of stearic acid and linolenic acid are updated based on products on the European market and are aligned with the requirements of the European legislation for food additives.

### Stavudine (2130)

**Assay - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Thiamine nitrate (0531)

**Identification:** in test C (nitrates), following confirmatory testing, new method introduced in order to avoid the use of nitrobenzene; this method is similar to the USP monograph.

### RRR- $\alpha$ -Tocopheryl acetate (1257)

**Related substances:** introduction of limits and relative retentions for the specified impurities and use of a CRS for their identification; system suitability requirements updated accordingly.

**Impurities:** section updated.

### Trimethoprim (0060)

**Definition:** minimum content limit tightened based on batch data received from manufacturers.

**Characters:** solubility in heptane added.

**Identification:** preparation of discs deleted from IR test.

**Related substances:** new UHPLC method introduced to replace the two previous LC tests; the new test covers impurities A to J and a new unspecified impurity (impurity L).

**Impurities:** section updated in accordance with the new test for related substances; names of impurities corrected.

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

**Peroxide value:** limit of 10 instead of 10.0, based on repeatability achieved.

**Assay, method B:** description of the column stationary phase aligned with the recommended columns given in the Knowledge database.

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

**Assay:** description of the column stationary phase aligned with the recommended column given in the Knowledge database. Grades of solvents amended in accordance with the Technical Guide (2022).

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

**Assay:** description of the column stationary phase aligned with the recommended column given in the Knowledge database. Grades of solvents amended in accordance with the Technical Guide (2022).

### Voriconazole (2576)

**Impurity E - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.

### Xanthan gum (1277)

**Total ash:** result expressed with reference to the dried substance.

### Xylose (1278)

**Second Identification:** test B modified in order to avoid the use of ethylene chloride R (REACH).

**Loss on drying:** milder vacuum conditions introduced.

### Zinc acetate dihydrate (1482)

**Identification A:** identification of acetates by odour (reaction a) has been replaced by a more suitable reaction (b).

### Ziprasidone mesilate trihydrate (2649)

**Assay - symmetry factor.** Default symmetry factor requirement (0.8-1.8) of revised general chapter 2.2.46 (Ph. Eur. 11<sup>th</sup> Edition) applied and previous requirement deleted from monograph.