

Comments concerning texts published in Supplement 11.2

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 Supplement 11.2 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 MONOGRAPHS

Monoclonal antibodies for human use (2031)

The monograph has been updated in accordance with the revised dosage form monograph *Parenteral preparations (0520)*, published in Ph. Eur. Supplement 10.5. It now refers directly to new general chapter 5.17.2 and includes the requirement 'practically free from visible particles' for liquid parenteral preparations, together with recommendations on testing for visible particles. It is to be noted that reference to chapter 5.17.2 in this monograph does not render the chapter mandatory in this context - chapter 5.17.2 states that: 'This general chapter is non-mandatory; it provides information on visible particle testing of liquid preparations that refer to general chapter 2.9.20. *Particulate contamination: visible particles in their monographs*'.

Production.

- *Statement that solutions for injection or infusion are practically free from particles included.*
- *Recommendations on testing for visible particles and reference to new general chapter 5.17.2 added.*

Tests. Appearance.

- *Compliance with general chapter 2.9.20 introduced.*
- *'Without visible particles' replaced with 'practically free from visible particles', while retaining the escape clause 'unless otherwise justified and authorised' (as currently expressed in the monograph). The intention of the 'practically free from visible particles' wording in the monograph Parenteral preparations (0520) is to indicate that the parenteral products in question should be free from such particles, but due to the impossibility of guaranteeing that testing will be 100 per cent accurate and that 100 per cent of particles will be detected, the qualifying term 'practically' had been inserted. The expression 'unless otherwise justified and authorised' (defined in the Ph. Eur. General Notices) has been intentionally kept for cases in*

which manufacturers can demonstrate that it is not possible to remove all visible particles, due to the inherent nature of monoclonal antibodies.

– *Recommendations on testing for visible particles and reference to new general chapter 5.17.2 added. It should be noted that this chapter also includes specific recommendations for the visual inspection - within quality control - of products administered using a filter (i.e., ‘With some parenteral products, for example products for which there is insufficient product knowledge, filters may be used to reduce the risks related to particles that may form during storage. However, the use of such filters does not constitute acceptance of particles after manufacture or allow particulate contamination per se. If justified and authorised, products administered using a filter can be exempt from the ‘practically free from particles’ requirement, providing it has been demonstrated that the filter delivers a filtrate that complies.’).*

– *Specific provisions for products administered using a final filter, as stated on the label, included.*

Labelling.

Statement that, where applicable, the solution is to be used with a final filter included.

VACCINES FOR VETERINARY USE

Clostridium botulinum vaccine for veterinary use (0360)

Potency test (section 3-4): addition of alternative end-points in line with monograph *Botulinum toxin type A injection* (2113). Once a laboratory has established the potency test, the lethal end-point is replaced by an observation of clinical signs and application of an end-point earlier than death to reduce animal suffering.

Batch potency test (section 2-3-1): cell-based assays specifically mentioned as a possible alternative.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Goldenrod (1892)

Identification C: TLC replaced by HPTLC in accordance with chapter 2.8.25.

Goldenrod, European (1893)

Identification C and test on *Solidago gigantea* Aiton and *Solidago canadensis* L.: TLC replaced by HPTLC in accordance with chapter 2.8.25.

Serratula coronata herb (2754)

Definition: content specification has been widened from minimum 5.0 per cent to minimum 0.50 per cent of β -ecdysterone ($C_{27}H_{44}O_7$; M_r 480.6) (dried drug). Based on the batch data received and data obtained from analysing different samples, it was concluded that the old

value of minimum 5.0 per cent was an error that had been introduced when the first version of the monograph was published.

MONOGRAPHS

Ascorbic acid (0253)

Related substances: change to quantitative style; new reference solution used for the quantification of impurity C to allow a more accurate quantification of this impurity.

Bupivacaine hydrochloride (0541)

Second identification: current test C deleted and current test E omitted since the remaining tests (i.e. TLC with double detection and reaction for chlorides) are considered sufficient for the purpose of the second identification. The letters used for the tests have been changed throughout the Identification section.

Impurity F: grades of solvents amended in accordance with Technical Guide (2015).

Calcium acetate (2128)

Chlorides, nitrates, sulfates: tests replaced by a unique ion chromatography method, as difficulties in the current test for nitrates have been reported by users.

Calcium ascorbate dihydrate (1182)

Title: degree of hydration added.

Identification: IR reference spectrum replaced by a CRS.

Related substances: introduction of an LC method and limits.

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

Impurities: addition of the section.

Calcium chloride dihydrate (0015)

Acidity or alkalinity: based on laboratory results, the colour obtained in the colour reaction has been changed from red to pink.

Calcium chloride hexahydrate (0707)

Acidity or alkalinity: based on laboratory results, the colour obtained in the colour reaction has been changed from red to pink.

Calcium pantothenate (0470)

Identification: test D modified in order to avoid the use of chloroform.

Clindamycin phosphate (0996)

Related substances: the preparation of reference solution (c) has been adjusted to take into account the new lyophilised form of the CRS, which can no longer be weighed but requires complete dissolution directly in its vial.

Clodronate disodium tetrahydrate (1777)

Related substances: test updated: separation between the substance to be examined and impurity D improved; quantitative determination of impurities.

Unspecified impurities: limit lowered to 0.05 per cent since the daily intake is potentially greater than 2 g.

Cyclophosphamide monohydrate (0711)

Second identification: tests C and D deleted since the mixed melting point is considered sufficient for the purpose of the second identification.

Ether (0650)

Test for substances with a foreign odour replaced by a GC procedure.

Test for Aldehydes replaced by the stricter test for Acetone and aldehydes.

Test for peroxides: duration increased to 30 min.

Flunarizine dihydrochloride (1722)

Identification: IR reference spectrum replaced by reference substance.

Related substances: impurity specifications updated to reflect the current quality of approved medicinal products on the European market; the limit for unspecified impurities introduced in line with requirements of the general monograph *Substances for pharmaceutical use* (2034).

Heparins, low-molecular-mass (0828)

Identification C: Following the introduction of Broad Standard Table calibration method in Supplement 9.8, the identification test has been further revised to include method system suitability criteria with the use of an in-house reference material. In addition to mass average molecular mass, other appropriate parameters are implemented in order to define molecular mass distribution.

Lysine acetate (2114)

Identification E: reaction (a) of acetates replaced by reaction (b). Reaction deleted from the first identification.

Ninhydrin-positive substances: the TLC replaced by an LC procedure to analyse amino acids.

Ammonium: test revised accordingly.

Miconazole nitrate (0513)

Related substances: impurities C, F and G are now specified in view of recent batch data from approved manufacturer on the European market.

Oxytocin (0780)

Definition: the chemical name of the substance was corrected.

Identification: nuclear magnetic resonance spectrometry (Identification B) was added as a possible alternative to amino acid analysis (Identification C).

Related substances: the description of the stationary phase was adjusted to indicate its end-capping and a particle size of 3 µm instead of 5 µm; the system suitability criterion was replaced with peak-to-valley ratio of minimum 2.0 between the peaks due to impurity D and to oxytocin; the oxytocin/desmopressin validation mixture CRS was replaced with *Oxytocin for peak identification CRS* for assessment of the system suitability criteria; *oxytocin impurity F CRS* was introduced; a paragraph on identification of impurities using CRSs was added; the retention time for oxytocin was adjusted and relative retentions for impurities with reference to oxytocin were introduced; limits for four specified impurities were introduced; the limit for any impurity was replaced with a limit for any other impurity and lowered to maximum 1.0 per cent; the limit for total impurities was adjusted from maximum 5 to maximum 5.0; the grades of solvents were amended in accordance with the Technical Guide (2015).

Water: the amount of substance was adjusted from 50 mg to 50.0 mg.

Impurities: a transparency section including 4 specified and 3 unspecified impurities was added.

Labelling: a statement on suitability of substance for use in manufacture of parenteral preparations was added.

Pemetrexed disodium 2.5-hydrate (3046)

Related substances, system suitability: a signal-to-noise ratio calculation has been added.

Pemetrexed disodium heptahydrate (2637)

Identification B: deleted since infrared absorption spectrophotometry is sufficiently specific.

Test for related substances:

- grade of solvents and stationary phase of the column used updated;
- correction factor for impurity D and signal to noise ratio calculation using reference solution (a) added.

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

Polysorbate 20 (0426)

Functionality-related characteristics: a section has been added; for polysorbate 20 used as emulsifier or solubiliser in liquid dosage forms (parenteral and non-parenteral) and in semi-solid preparations, cross-reference to composition of fatty acids and hydroxyl value added.

Polysorbate 40 (1914)

Functionality-related characteristics: a section has been added; for polysorbate 40 used as emulsifier or solubiliser in liquid dosage forms (parenteral and non-parenteral) and in semi-solid preparations, cross-reference to composition of fatty acids and hydroxyl value added.

Polysorbate 60 (0427)

Functionality-related characteristics: a section has been added; for polysorbate 60 used as emulsifier or solubiliser in liquid dosage forms (parenteral and non-parenteral) and in semi-solid preparations, cross-reference to composition of fatty acids and hydroxyl value added.

Polysorbate 80 (0428)

Functionality-related characteristics: a section has been added (considered as local requirements); for polysorbate 80 used as emulsifier or solubiliser in liquid dosage forms (parenteral and non-parenteral) and in semi-solid preparations, cross-reference to composition of fatty acids and hydroxyl value added.

Prednisone (0354)

Impurities: impurities F and G deleted from the transparency list as they are of unknown structure, not identified by a CRS and covered by the limit for unspecified impurities.

Promazine hydrochloride (1365)

Related substances: TLC replaced by new LC method covering three additional impurities.

Impurities: section updated.

Propylthiouracil (0525)

Identification. Identifications A and D deleted, remaining tests are sufficient.

Impurity A and Related substances: TLC procedure replaced by 2 different LC procedures, one covering impurity A and the other covering other related substances.

Assay: upper limit widened.

Riboflavin sodium phosphate hydrate (0786)

Title: hydrate added.

Definition, structure and nomenclature: updated to take into account both the monophosphate and the diphosphate derivatives.

Identification: UV and LC identifications have been replaced by IR, which is specific enough.

Related substances: addition of a limit for unspecified impurities and for the total and introduction of a *riboflavin for peak identification CRS* to identify impurities F, G and H.

Composition: test introduced to set a minimum value for the main component and maximum values for the minor components.

Loss on drying: replacement of the given value for vacuum pressure by “*in vacuo*”.

Inorganic phosphate: limit decreased based on available batch data.

Impurities: as diphosphate derivatives are now listed as minor components, impurities A, B and C have been deleted; list of impurities updated.

Salmeterol xinafoate (1765)

Related substances: description of reference solution (a) amended following a change in the production of CRS material.

Sodium ascorbate (1791)

Related substances: change to quantitative style; new reference solution used for the quantification of impurity C to allow a more accurate quantification of this impurity.

Sodium starch glycolate (type A) (0983)

Settling volume: the standing time was increased to 4 h to allow all particle fractions to settle.

Sodium starch glycolate (type B) (0984)

Settling volume: the standing time was increased to 4 h to allow all particle fractions to settle.

Somatropin (0951)

This revision is part of a larger exercise in which all somatropin monographs, i.e. *Somatropin concentrated solution (0950)*, *Somatropin (0951)*, *Somatropin powder for injection (0952)* and *Somatropin injection (2370)* were revised simultaneously and, where possible, harmonised. All the revised monographs are published in the same Supplement (11.2).

Related proteins: The analytical procedure was replaced with the procedure already described in *Somatropin injection (2370)* monograph and that is capable of detecting more of oxidised forms. In combination with the CZE detection of deamidated forms, this approach proves superior for the control of related proteins.

Charged variants: due to a change in formulation between batch 3 and batch 4 of *Somatropin CRS*, the solvent used to reconstitute this CRS was changed to tris-hydrochloride buffer to ensure adequate dissolution.

Somatropin concentrated solution (0950)

This revision is part of a larger exercise in which all somatropin monographs, i.e. *Somatropin concentrated solution (0950)*, *Somatropin (0951)*, *Somatropin powder for injection (0952)* and *Somatropin injection (2370)* were revised simultaneously and, where possible, harmonised. All the revised monographs are published in the same Supplement (11.2).

Related proteins: The analytical procedure was replaced with the procedure described in *Somatropin injection (2370)* monograph and that is capable of detecting more of oxidised forms. In combination with the CZE detection of deamidated forms, this approach proves superior for the control of related proteins.

Charged variants: due to a change in formulation between batch 3 and batch 4 of *Somatropin CRS*, the solvent used to reconstitute this CRS was changed to tris-hydrochloride buffer to ensure adequate dissolution.

Somatropin injection (2370)

This revision is part of a larger exercise in which all somatropin monographs, i.e. *Somatropin concentrated solution (0950)*, *Somatropin (0951)*, *Somatropin powder for injection (0952)* and *Somatropin injection (2370)*, were revised simultaneously and, where possible, harmonised. All the revised monographs are published in the same Supplement (11.2).

Title: The title was changed to reflect the fact that the monograph covers a medicinal product for injection.

Definition: Reference to *Parenteral preparations (0520)* was introduced to highlight that this general monograph was also applicable.

Related proteins: The note indicating that the test excluded deamidated forms was deleted as the latter were partially detected by the test. The autosampler temperature was added. The reagents used to describe the stationary phase were modified. The grades of solvents were amended in accordance with the Technical Guide (2015). Due to a change in formulation between batch 3 and batch 4 of *Somatropin CRS*, the solvent used to reconstitute this CRS was changed to phosphate buffer to ensure adequate dissolution.

Deamidated forms: due to a change in formulation between batch 3 and batch 4 of *Somatropin CRS*, the solvent used to reconstitute this CRS was changed to tris-hydrochloride buffer to ensure adequate dissolution.

Somatropin powder for injection (0952)

This revision is part of a larger exercise in which all somatropin monographs, i.e. *Somatropin concentrated solution (0950)*, *Somatropin (0951)*, *Somatropin powder for injection (0952)* and *Somatropin injection (2370)* were revised simultaneously and, where possible, harmonised. All the revised monographs are published in the same Supplement (11.2).

Title: The title was changed to reflect the fact that the monograph covers a medicinal product supplied as a powder for injection.

Production: Production of somatropin powder for injection without the isolation of an intermediate of the solid or liquid bulk is no longer current practice; all references to this aspect have therefore been deleted. This includes deletion of Host-cell-derived proteins and Host-cell- and vector-derived DNA tests, covered at the level of monographs on somatropin active substance, i.e. *Somatropin concentrated solution (0950)* or *Somatropin (0951)*.

Identification: In accordance with the changes in the Production section, Identifications A and C were deleted, harmonising the approach with monograph *Somatropin injection (2370)*.

Related proteins: The analytical procedure was replaced with the procedure described in *Somatropin injection (2370)* monograph and that is capable of detecting more of oxidised forms. In combination with the CZE detection of deamidated forms, this approach proves superior for the control of related proteins.

The limit of maximum 13.0 per cent was not justified since a tighter limit of maximum 10 per cent was set for the more degradation-prone medicinal product form covered by the *Somatropin injection (2370)* monograph. It was therefore tightened to maximum 10 per cent in accordance with the results collected during the revision process of this monograph.

Charged variants: due to a change in formulation between batch 3 and batch 4 of *Somatropin CRS*, the solvent used to reconstitute this CRS was changed to tris-hydrochloride buffer to ensure adequate dissolution.

Starch, hydroxypropyl (2165)

Functionality-related characteristics: a section has been added; for hydroxypropyl starch used as film former in oral solid dosage forms, cross-reference to hydroxypropyl groups content and appearance of a film.

Starch, hydroxypropyl, pregelatinised (2645)

Functionality-related characteristics: a section has been added; for hydroxypropyl starch pregelatinised used as film former in oral solid dosage forms, cross-reference to hydroxypropyl groups content and appearance of a film.

Thiopental sodium and sodium carbonate (0212)

Graphic and molecular formulas: sodium carbonate added.

CAS number: added for thiopental sodium only.

Characters: solubility in heptane added.

Identification: test D deleted, since the remaining tests are considered sufficient for the purpose of the second identification.

pH: test added.

Related substances: reagent used to describe stationary phase modified; grade of acetonitrile in mobile phase amended in accordance with Technical Guide (2015); correction factor of impurity B updated and correction factor of impurity D added; limits expressed in the quantitative style.

Thiopental assay: titrimetric method replaced by LC method used in related substances test.

Impurities: section updated.

Titanium dioxide (0150)

Elemental impurities: based on batch data, the limit for antimony has been increased to maximum 20 ppm.

Yohimbine hydrochloride (2172)

Related substances. Two different CRSs have been described, one for identification by IR and assay and the other one for system suitability and identification of the specified impurities.