

COMMENTS CONCERNING SOME REVISED/CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 6.3

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the November 2007 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

GENERAL TEXTS

2.2.33. Nuclear magnetic resonance spectrometry

This general method has been completely revised in order to take account of the different techniques currently applied in the analysis of pharmaceutical substances.

2.2.42. Density of solids

Bulk and tapped density: due to the adoption of the harmonised text Bulk density and tapped density of powders (2.9.34), the reference to Apparent volume (2.9.15) is replaced by a reference to chapter 2.9.34.

2.5.24. Carbon dioxide in gases

2.5.25. Carbon monoxide in gases

The general chapter has been revised to take into account the following considerations:

- all infrared analysers are based on the same general measuring principle: an infrared beam passes through a cell containing the gas to be examined and a detector measures the quantity of residual energy in the beam;
- apparatus with 2 infrared sources, such as those described in the Ph. Eur., are no longer commercialised. Although they are still widely used in control laboratories, they will progressively disappear as this type of apparatus is replaced;
- the addition of minimum performance criteria was necessary.

2.5.27. Oxygen in gases

Method 2.5.27 is used to assay oxygen in gases, in particular in *Medicinal air (1238)*, *Synthetic medicinal air (1684)* and *Oxygen (0417)*.

According to the operating conditions described in the 6th Edition, the calibration of the apparatus is carried out by passing through air that contains 20.9 per cent V/V O₂. Using oxygen of a defined purity gives better accuracy; *oxygen R* is therefore now used instead of air as the reference standard gas.

2.6.1. Sterility

The general chapter is part of the international harmonisation programme. A first text was signed-off by the PDG in 2002, including a number of residual differences. Following a Q4B recommendation for further harmonisation, the text has undergone the following major revision.

Precautions against microbial contamination: reference to EU GMP has been deleted.

Culture media and incubation temperature:

- the possibility to use other media has been deleted; the use of alternative methods is covered by General Notices;
- the moisture content of the agar has been removed;
- the possibility to use fluid thioglycollate medium instead of soya-bean casein digest medium for products containing mercurial preservatives has been added; a provision for use of this medium is given (the medium

- is validated as described in the growth promotion test);
- the possibility to use an alternative thioglycollate medium where prescribed or justified and authorised has been added (this medium is sometimes used in case of turbidity or viscosity of the sample, e.g. whole blood);
- the term ‘validation’ has been replaced by the more appropriate term ‘method suitability’.

Test for sterility of the product to be examined:

- the description of the maximum washing cycle has been clarified;
- the minimum number of items to be tested for large-volume parenterals has been decreased to 10.

Guidelines for using the test for sterility: this section, which is not part of international harmonisation, has been deleted from the chapter and included in section 5 of the European Pharmacopoeia.

2.6.12. Microbiological examination of non-sterile products: microbial enumeration tests

2.6.13. Microbiological examination of non-sterile products: test for specified micro-organisms

As of 1 January 2009 and in agreement with the EMEA (see <http://www.emea.europa.eu/Inspections/QWPfaq.html>), the 1st set of tests will be phased out. Users will have to apply the 2nd set of tests (harmonised method) only as the Ph. Eur. reference method.

2.7.2. Microbiological assay of antibiotics

The adoption of the monograph *Teicoplanin (2358)* leads to the revision of this general chapter, with a modification of Table 2.7.2.-1 and the introduction of a new culture medium (medium H).

2.9.1. Disintegration of tablets and capsules

Test A apparatus: this minor revision to the disc dimensions takes account of the revised international harmonisation text.

2.9.33. Characterisation of crystalline and partially crystalline solids by X-ray powder diffraction (XRPD)

This chapter is revised to take account of the international harmonisation text.

5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use

As of 1 January 2009 and in agreement with the EMEA (see <http://www.emea.europa.eu/Inspections/QWPfaq.html>), the 1st set of criteria will be phased out. Users will have to apply the 2nd set of criteria (harmonised method) only as the Ph. Eur. reference method.

5.1.5. Application of the F_0 concept to steam sterilisation of aqueous preparations

The word ‘theoretical’ needs to be added to the *Z*-value, so as to avoid misunderstandings as to the actual *Z*-values found for *Geobacillus stearothermophilus*.

5.1.9. Guidelines for using the test for sterility

These guidelines were previously a non-mandatory part of chapter 2.6.1 and are not the subject of international harmonisation. In order to avoid confusion among users or evaluators of interchangeability, these guidelines are moved to a non-mandatory part of the European Pharmacopoeia.

Guidance on the minimum number of items to be tested is now a mandatory part of 2.6.1.

5.2.3. Cell substrates for the production of vaccines for human use

Retroviruses: testing by product-enhanced reverse

transcriptase (PERT) and transmission electron microscopy (TEM) are prescribed and if a positive result is obtained in either test, infectivity assays are prescribed with a PERT read-out on the supernatant.

Since the PERT method is about a million-fold more sensitive than infectivity assays, a paragraph on the interpretation of results obtained is added.

This test scheme takes advantage of the much better limit of detection of PERT, with a safeguard against false positives via the infectivity assays.

GENERAL MONOGRAPHS**Substances for pharmaceutical use (2034)**

Definition: the scope of the monograph was previously limited to substances for which there is an individual monograph in the Pharmacopoeia; this revision extends the scope to all substances for pharmaceutical use, but allows for the possibility of an exception for substances used in the manufacture of medicinal products for the special needs of individual patients, where this is justified by risk assessment; exceptions are also introduced for homoeopathic products.

Production: a paragraph has been added indicating that the processing of active substances with excipients is considered to be a pharmaceutical manufacturing operation that must be carried out in GMP conditions.

Vaccines for human use (0153)

Inactivation: validation against a panel of model viruses is specified for products that may have extraneous agents in the harvest, for example those produced in eggs from healthy, non-SPF flocks; this is in line with current practice.

Labelling: where a vaccine is adsorbed, this must be stated on the label; the monograph title will usually suffice, but for vaccines that may be presented with or without an adsorbent, the monograph title does not comprise 'adsorbed' and a distinct statement is needed, by modification of the vaccine title to include the word 'adsorbed' or otherwise.

Adjuvants: quality requirements regarding adjuvants have been added (in line with EMEA guideline 134716/2004).

Appearance: it is now stated that each container of each final lot is visually inspected except in justified and authorised cases.

Bacterial endotoxins: since it is current practice to carry out a bacterial endotoxin test on each final product, such a test has been added in the general monograph, and the limit is either specified in the individual monograph or approved by the competent authority.

DOSAGE FORMS**Powders for cutaneous application (1166)**

Fineness: due to the adoption of the harmonised text Powder fineness (2.9.35), the reference to chapter 2.9.12 is replaced by a reference to chapter 2.9.35.

Semi-solid preparations for cutaneous application (0132)

Uniformity of dosage units. According to the definition in the monograph, semi-solid preparations are intended for local or transdermal delivery. Some pharmaceutical products (in particular hormone-based products) can

be found in the form of semi-solid preparations for transdermal release. Supplying them in single-dose containers is intended to improve compliance, and the content of a single-dose container corresponds to a precise dose of the medicinal product. It was therefore necessary to introduce into the monograph a test for uniformity of dosage units (2.9.40) for single-dose preparations intended for transdermal delivery and for which the entire contents correspond to one dose of the medicinal product.

VACCINES FOR HUMAN USE**BCG for immunotherapy (1929)**

Temperature stability: the test has been deleted; when used as a batch test, temperature stability may be seen as a check on the freeze-drying process and a predictor of long-term stability, but experience indicates that it has no added value compared with stability studies that are obligatory during development of the product.

Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2065)

Scope: the monograph has been revised in order to extend its scope to vaccines where the haemophilus

component is pre-integrated in the liquid preparation.

Bacterial endotoxins: the limit of 100 IU has been deleted; the limit is decided by the competent authority; some existing products do not comply with the limit of 100 IU but have been found to be safe.

Free PRP: the paragraph has been expanded to take account of currently used methods.

Haemophilus type b conjugate vaccine (1219)

Volatile matter, including water: since the cited method used to determine volatile substances, i.e. thermogravimetry, can be replaced advantageously by other methods such as a combination of micro-

determination of water (2.5.32) and a specific determination of solvents by gas chromatography (2.2.28), no particular method is cited as an example anymore.

Ribose and Phosphorus: since ribose and phosphorus contents are calculated with reference to the dried substance, the residual moisture affects these results; while no reference method for the determination of water is given, ribose and phosphorus contents are within the limits approved by the competent authority for the particular product.

Free PRP: the paragraph has been expanded to update to currently used methods.

Poliomyelitis vaccine (inactivated) (0214)

Inactivation. A test for inactivation was previously required at 2 production stages: the 1st at the monovalent harvest stage and the 2nd at the trivalent pool of monovalent harvests stage or the final bulk stage. This monograph has been revised in order to delete the 2nd inactivation test and to replace it by a requirement to test the inactivation kinetics on each batch of monovalent harvest to show consistency of the inactivation process. In addition, this revision contains a requirement to use

for this test cells that have shown optimal sensitivity to residual infectious poliovirus (as already recommended by the WHO). This provides further assurance that the single test will provide a security level that is at least equivalent to the 2 tests previously required. It should also be noted that the remaining inactivation test is performed at a stage (monovalent harvest, before any further blending and dilution) where maximum sensitivity is to be expected.

Varicella vaccine (live) (0648)

Definition: the nomenclature of the virus has been corrected.

Production: the defined maximum passage level for the vaccine strain has been deleted; the use up to the 38th passage referred to the Oka strain, and during a previous revision of the monograph the restriction to the Oka strain was removed but the maximum passage number was inadvertently left in the monograph.

Water: the defined limit (3 per cent) has been deleted since, in light of stability data, different products are authorised with different limits; in consequence, the test has been moved to the Production section since it cannot be carried out by an independent analyst.

RADIOPHARMACEUTICAL PREPARATIONS

Technetium (^{99m}Tc) colloidal rhenium sulphide injection (0126)

Technetium (^{99m}Tc) macrosalb injection (0296)

Technetium (^{99m}Tc) microspheres injection (0570)

Technetium (^{99m}Tc) tin pyrophosphate injection (0129)

Pyrogen: this test has been replaced by a test for bacterial endotoxins in order to avoid animal testing.

MONOGRAPHS

Acacia (0307)

Acacia, spray-dried (0308)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse (non-parenteral use).

N-Acetyltryptophan (1383)

Related substances: 1,1'-ethylidenebistryptophan CRS is produced by evaporation. Preparation of reference solutions (b) and (c) have been modified accordingly. A maximum value of 3.5 has been added for the symmetry factor.

Adenosine (1486)

Related substances: the TLC has been deleted as impurities C, D and E are 'theoretical' and are not present in the substance, and ribose (impurity B) does not need to be specifically controlled.

Impurities: specified impurities B, C, D and E deleted.

Agar (0310)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Air, medicinal (1238)

Oil: some countries have phased out, the use of the extraction solvent C₂Cl₃F₃ because Regulation (EC) No

2037/2000 prescribes a schedule for phasing out the production of chloro-fluorohydrocarbons. No other suitable solvent could be found. The control of the oil content is now made using oil detector tubes (Production and Tests). Such a test is only relevant when the gas is produced using an oil-lubricated compressor.

Alginic acid (0591)

Almagate (2010)

Aluminium magnesium silicate (1388)

Aluminium oxide, hydrated (0311)

Aluminium phosphate gel (2166)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Amphotericin B (1292)

Characters: it has been added that the substance is hygroscopic.

Identification: IR and the LC described for the test for related substances are sufficient as first identification.

Related substances: a test by LC has been introduced replacing the old test for content of tetraenes.

Aprotinin (0580)

Aprotinin concentrated solution (0579)

Production: the sentence on contamination has been deleted, in line with modifications adopted in all monographs covering biological substances of human or animal origin.

Identification A: the preparation of reference solution has been modified.

Protein impurities of higher molecular mass: this test has been replaced by:

- a capillary zone electrophoresis for the detection of des-Ala-aprotinin and des-Ala-des-Gly-aprotinin;
- a LC for the detection of pyroglutamyl-aprotinin and related compounds;
- a new size-exclusion chromatography for the detection of aprotinin oligomers.

Assay: glass-silver-silver chloride electrodes are proposed as an alternative to glass and calomel electrodes.

Labelling: the indication concerning the manufacture of parenteral preparations has been added.

Impurities: a section describing the impurities has been introduced.

Ascorbic acid (0253)

Identification B: the description of the sample preparation has been deleted in accordance with current policy.

Related substances: an LC has been introduced in accordance with current policy as part of a special revision programme.

Impurities: a section has been added.

Beclometasone dipropionate, anhydrous (0654)

Related substances: an improved LC method with a gradient has been introduced which allows a better separation and control of the impurities. The limits have been reviewed to reflect the quality of the substances used in approved medicinal products in Europe.

Beclometasone dipropionate monohydrate (1709)

Related substances: an improved LC method with a gradient has been introduced which allows better separation and control of the impurities. However, as the monohydrated substance is purer, limits and specified impurities are not the same as for *anhydrous beclometasone dipropionate* (0654).

Belladonna leaf dry extract, standardised (1294)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Bentonite (0467)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Betamethasone valerate (0811)

Identification: the set of tests used for identification has been simplified; the chloroform used as a solvent for IR recrystallisation has been replaced by the less-toxic methylene chloride.

Specific optical rotation: dioxan (class 2 solvent) has been replaced by anhydrous ethanol (class 3 solvent).

Related substances: the existing LC has been amended to improve the separation of betamethasone valerate and its impurities.

Impurities: a section describing the impurities controlled by the modified LC has been introduced.

Bitter-orange epicarp and mesocarp (1603)

Identification B: illustration of the powdered drug added.

Bitter-orange flower (1810)

Identification B: illustration of powdered drug added. Concentration of mounting solution decreased and acceptance criterion modified.

Calcium Folate (0978)

Chlorides: method has been replaced by that currently published in the monograph for *calcium levofolate pentahydrate* (1606).

Calcium gluconate (0172)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Calcium gluconate for injection (0979)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. The tests for specified micro-organisms have been deleted because Gram-negative contamination is covered by a test for bacterial endotoxins in the monograph, and for *Staphylococcus aureus* no significance of its limitation has been confirmed.

Calcium stearate (0882)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse.

Cellulose acetate (0887)

Definition: deletion of the limits for acetyl groups, typical values of which are now indicated under functionality-related characteristics (FRCs).

Identification: comparison made using a CRS instead of a reference spectrum, in accordance with current policy.

Free acid: editorial changes to reflect the international harmonisation document.

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Assay for acetyl groups: this assay is a relevant control parameter for functions of the substance, and has therefore been moved to the FRCs section.

Labelling: deleted due to the addition of the FRCs section.

Functionality-related characteristics: apart from viscosity and degree of substitution (acetyl groups), molecular mass distribution, particle-size distribution and powder flow are considered useful in view of the formulation.

Cellulose acetate phthalate (0314)

Identification: comparison made using a CRS instead of a reference spectrum, in accordance with current policy.

Free acid: changes in the wording have been approved in the framework of international harmonisation.

Phthaloyl groups: changes in the wording have been approved in the framework of international harmonisation. This test, as well as that for acetyl groups, are relevant control parameters for functions of the

substance and have been moved to the functionality-related characteristics (FRC) section.

Viscosity: this test has been moved to the FRC section.

Cellulose, microcrystalline (0316)

Cellulose, powdered (0315)

Charcoal, activated (0313)

Chondroitin sulphate sodium (2064)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Cisplatin (0599)

Identification A: the description of the sample preparation has been deleted in accordance with current policy.

Related Substances: an LC method has been developed in replacement of the TLC to quantify transplatin (impurity A) and aminetrichloroplatinate (impurity B) in the same run.

Impurities: a section describing the impurities controlled by the LC has been introduced.

Cod-liver oil (Type A) (1192)

Cod-liver oil (type B) (1193)

Definition: the obtention from wild cod has been indicated, since a monograph on oil from farmed cod is published.

Characters: deletion of 'viscous' appearance.

Stearin: the method has been improved to take account of the possible presence of solid matters in the oil.

Vitamin A and Vitamin D₃: the system suitability test criteria of both assays have been reviewed and modified; in particular, the 2nd criterion has been replaced because it did not give a true indication of the validity of the assay. Furthermore, the conversion factor for the specific absorbance of all-trans-retinol has been corrected in the test for vitamin A.

Croscarmellose sodium (0985)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Crospovidone (0892)

Identification: comparison made using a CRS instead of a reference spectrum, in accordance with current policy; the former identification test D, the results of which were difficult to evaluate, has been replaced by a determination of the screening residue after wet sieving.

Functionality-related characteristics: a section has been added for crospovidone used as disintegrant or as suspension stabiliser. In the 1st case, hydration capacity is the fundamental test, expressing the capacity of the polymer to soak water. Particle-size distribution and Powder flow are also useful in view of the formulation.

Crospovidone is also available as a micronised form, which is used as suspension stabiliser. Settling volume is proposed in this case.

Dextran 1 for injection (1506)

Dextran 40 for injection (0999)

Dextran 60 for injection (1000)

Dextran 70 for injection (1001)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. For preparations used parenterally, tests for specified micro-organisms are deleted, since a test for bacterial endotoxins is systematically prescribed and since the final product must be sterile; only a TAMC should be given.

Erythritol (1803)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Ferrous gluconate (0493)

Frangula bark dry extract, standardised (1214)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Galactose (1215)

Gelatin (0330)

Glucose, liquid, spray-dried (1525)

Guar (1218)

Guar galactomannan (0908)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Haemodialysis solutions, concentrated, water for diluting (1167)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Hard fat (0462)

Identification. Some hard fat grades marketed in Europe show a very low content of diglycerides and monoglycerides. The TLC identification does not allow the detection of these minor components although these grades comply with the other specifications of the monograph. In this case the tests for melting point and hydroxyl value are required in addition to the TLC identification.

Human normal immunoglobulin for intravenous administration (0918)

Immunoglobulin A: since the maximum content of immunoglobulin A (IgA) must be indicated on the label, a test has been added requiring determination by a suitable immunochemical method.

Human plasma (pooled and treated for virus inactivation) (1646)

Hepatitis A virus antibodies: the limit for hepatitis A virus antibodies has been lowered from 2 IU/ml to 1.0 IU/ml because it has been observed that this antibody level has been decreasing in the population of some countries over the last few years and this could lead to supply problems.

Hepatitis A virus RNA: in view of the change to the requirement for hepatitis A virus antibodies, a limit for the hepatitis A virus load in the plasma pool using a

nucleic acid amplification test has been introduced with a positive control of 1.0×10^2 IU/ml of hepatitis A virus RNA.

Hepatitis C virus RNA: the limit is expressed as 1.0×10^2 instead of 100 to avoid unjustified rounding.

Factor V: a statement regarding the definition of the unit has been deleted since an International Standard has been added.

Plasmin inhibitor: a statement regarding the definition of the unit has been added; human normal plasma is used to define the unit since no International Standard is yet available.

Hydroxypropylbetadex (1804)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Kaolin, heavy (0503)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Lactitol monohydrate (1337)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Lactose, anhydrous (1061)

Lactose monohydrate (0187)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Functionality-related characteristics/Bulk and tapped density: further to the adoption of the harmonised text, the reference to chapter 2.9.15 is replaced by a reference to chapter 2.9.34.

Lactulose (1230)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Lactulose, liquid (0924)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used; TYMC 10¹ is mentioned because this is the actual drug product and a contamination might occur.

Lauromacrogol 400 (2046)

Lauromacrogol 400 corresponds to macrogol lauryl ether with 9 ethylene oxide (EO) moles per mole of substance. The monograph *Macrogol lauryl ether (1124)* is already included in the Ph. Eur., covering grades having 3 to 23 EO moles per mole of substance. These grades are used as excipients. This monograph covers macrogol lauryl ether with 9 EO units used as active substance, mainly for vein sclerosis. The quality control tests prescribed are therefore more sophisticated: tests for free lauryl alcohol and free macrogols have been added as well as a test by NMR (average number of EO moles and

average chain length of the fatty alcohol). Assay methods have been tested but proved to be non-satisfactory.

Levodropropizine (1535)

Identification: a cross reference to the LC test for enantiomeric purity has been added as alternative to the test for specific optical rotation.

Impurity B and related substances: the method has been modified in order to improve the sensitivity and the separation of the impurities. In accordance with the impurity policy, a limit for total impurities has been added.

Impurities B and C: in accordance with current policy, the reference substance for quantification of impurities B and C are described as CRS and either like reagents (R).

Enantiomeric purity: the precision of the quantity of *levodropropizine* CRS has been modified for preparation of reference solution (a).

Lynestrenol (0558)

Identification: 2nd identification not of practical relevance for this substance, so identification tests A and C no longer prescribed.

Related substances: TLC replaced by GC in accordance with current policy, as part of a special revision programme.

Impurities: section introduced describing impurities controlled by GC.

Magnesium carbonate, light (0042)

Magnesium oxide, heavy (0041)

Magnesium oxide, light (0040)

Identification A: due to the adoption of the harmonised text on *Bulk density and tapped density of powders (2.9.34)*, the monograph has been revised to no longer express the criterion as apparent volume (2.9.15) but as bulk density.

Magnesium stearate (0229)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse.

Maize starch (0344)

Identification A: the crossed nicol prisms are replaced by orthogonally orientated polarising plates or prisms, used nowadays in practice; the identification section is harmonised and the change has been agreed within the PDG.

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse.

Maltitol (1235)

Maltodextrin (1542)

Mannitol (0559)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Mefenamic acid (1240)

Identification: as the 2nd identification is not necessary, identifications A, C and D have been deleted; the description of the sample preparation has been deleted in accordance with current policy.

Related substances: TLC has been replaced by LC in accordance with current policy.

2,3-Dimethylaniline: this substance is now detected by the revised test for related substances.

Impurities: specified impurities C and D and unspecified impurity E have been added.

Methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent (1129)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Methotrexate (0560)

Assay: the concentrations of test solution (b) and reference solution (a) have been decreased to obtain a peak shape that complies with the symmetry requirement.

Mianserin hydrochloride (0846)

Identification B: the description of the sample preparation has been deleted in accordance with current policy.

Related substances: TLC replaced by LC in accordance with current policy.

Impurities: section describing impurities controlled by LC added.

Nicotine (1452)

Nicotine resinate (1792)

Related substances: the method has been replaced by a gradient LC which gives better resolution of structurally similar compounds and reduces peak broadening.

Olive leaf (1878)

Identification B: illustration of the powdered drug added.

Assay: preparation of test solution modified to allow use of ISO glassware.

Omega-3-acid ethyl esters 60 (2063)

Definition: harmonised with that of monographs on similar products; the use of additional antioxidants is permitted to facilitate the use of the substance in dosage forms other than soft capsules, such as liquid preparations for oral use.

Anisidine value: cross-reference is made to the general chapter.

Oligomers and partial glycerides: a differential refractometer is used for detection, and such detectors differ in sensitivity; in addition, small variations in temperature and flow rate may reduce the signal-to-noise ratio; a more concentrated test solution is therefore required; furthermore, the 3rd requirement for system suitability is deleted.

EPA and DHA ethyl esters: reference to the chromatogram is specified for identification of the peaks.

Omega-3-acid ethyl esters 90 (1250)

Definition: harmonised with that of monographs on similar products.

Identification A: reference to peak size deleted.

Identification B: to harmonise with the monograph *Omega-3-acid ethyl esters 60 (2063)*, a cross-reference to the assay for total omega-3-acid ethyl esters is added.

Oligomers: a differential refractometer is used for detection, and such detectors differ in sensitivity; in addition, small variations in temperature and flow rate may reduce the signal-to-noise ratio; a more concentrated test solution is therefore required.

Assay: a new chromatogram is provided.

EPA and DHA ethyl esters: reference to the chromatogram is specified for identification of the peaks.

Omega-3-acid triglycerides (1352)

Definition: harmonised with that of monographs on similar products; the use of additional antioxidants is permitted to facilitate the use of the substance in dosage forms other than soft capsules, such as liquid preparations for oral use.

Identification: reference to peak size deleted.

Anisidine value: cross-reference is made to the general chapter.

Oligomers and partial glycerides: a differential refractometer is used for detection, and such detectors differ in sensitivity; in addition, small variations in temperature and flow rate may reduce the signal-to-noise ratio; a more concentrated test solution is therefore required.

EPA and DHA: reference to the chromatogram is specified for identification of the peaks.

Oxaliplatin (2017)

Related substances, impurity B: due to the low solubility of impurity B, it is necessary to sonicate for 1.5 h to obtain a solution.

Oxymetazoline hydrochloride (0943)

Related substances: TLC has been replaced by LC in accordance with current policy; this test has been harmonised with the current monograph for xylometazoline hydrochloride (1162).

Impurities: other detectable impurities have been added.

Paclitaxel (1794)

Related substances: *acetonitrile R* is replaced throughout by *acetonitrile R1*; reference solution (d) in test B has been modified as *paclitaxel semi-synthetic for system suitability CRS* is produced by evaporation.

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. The tests for specified micro-organisms have been deleted because Gram-negative contamination is covered by a test for bacterial endotoxins in the monograph. The test for *Staphylococcus aureus* has been deleted as the need for this limit has not been confirmed.

Pancreas powder (0350)

Pepsin powder (0682)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Perphenazine (0629)

Identification: the 2nd identification is not of practical relevance for this substance, so identifications B and D are no longer prescribed.

Related substances: the TLC has been replaced by an LC in accordance with current policy.

Impurities: a section describing the impurities controlled by the LC has been added.

Polyacrylate dispersion 30 per cent (0733)**Poly(vinyl acetate) dispersion 30 per cent (2152)**

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Potassium citrate (0400)

Test for water: results were not reproducible with the previous method which has been corrected by using a mixture of *methanol R* and *formamide R* as solvent; the sample size has been adjusted to allow the use of a 5 ml burette.

Potato starch (0355)

Identification A: the crossed nicol prisms are replaced by orthogonally orientated polarising plates or prisms, used nowadays in practice; the identification section is harmonised and the change has been agreed within the PDG.

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse.

Pravastatin sodium (2059)

Related substances: the current method covers the additional impurity F which has been included as a specific impurity.

Rice starch (0349)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse.

Senna leaf dry extract, standardised (1261)**Sodium alginate (0625)**

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Sodium ascorbate (1791)

Identification B: the description of the sample preparation has been deleted in accordance with current policy.

Related substances: an LC has been introduced in accordance with current policy as part of a special revision programme, and in harmonisation with the monograph *Ascorbic acid (0253)*.

Benzene: the test has been deleted because the solvent is now controlled by chapter 5.4 *Residual solvents*.

Impurities: a section has been added.

Sodium glycerophosphate, hydrated (1995)

Definition: sodium glycerophosphate hydrated usually contains up to 12 per cent of sodium glycerol diphosphate and up to 2 per cent of sodium glycerol triphosphate. The definition has been revised to take into account the presence of di and tri-phosphates. As a consequence, limits have been adjusted to the new definition.

Sodium hyaluronate (1472)

Microbial contamination: the implementation of the

internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Sodium polystyrene sulphonate (1909)

Microbial contamination: a new style is used for expressing the acceptance criteria.

Sodium stearate (2058)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse (non-parenteral use).

Sorbitol (0435)**Sorbitol, liquid, partially dehydrated (2048)**

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Starch, pregelatinised (1267)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse.

Sucrose (0204)

A sign-off document of the PDG has been issued for this monograph within the framework of international harmonisation.

Solution S: it is now prepared with *water R*. This is not a problem for the tests in which solution S is used.

Conductivity: the temperature of measurement is specified as it is different from that in the general method.

Lead: batch data on about 250 batches tested over the past 10 years show results under the detection limit of 0.03 ppm or close to it. The contribution compared to total dietary intake is not significant and the European Commission Regulation (EC) n° 466/2001 setting maximum levels for certain contaminants in foodstuffs does not contain any limit for lead or other heavy metals in sucrose. For those reasons, the test for lead has been deleted.

Sugar spheres (1570)

Fineness: following the adoption of the harmonised text, the reference to chapter 2.9.12 has been replaced by a reference to chapter 2.9.35.

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Sumatriptan succinate (1573)

Impurities A and H: relative retentions introduced; system suitability criterion for resolution replaced by a resolution between the more critical pair of peaks, impurities A and H; correction factor for impurity A introduced.

Related substances: relative retentions of specified impurities added.

Talc (0438)

Lead: for the purpose of international harmonisation the limit is specified as 1.0×10^1 ppm.

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Tetracosactide (0644)

This monograph has undergone general and extensive revision, the most significant change being the replacement of the bioassay by a LC.

Related peptides: improved LC introduced; former test B (TLC) deleted.

Water: semi-micro determination replaced by coulometric titration, which uses a smaller amount of test sample.

Bacterial endotoxins: test added, in line with the general policy for peptide monographs, with a limit based on batch results.

Assay: bioassay on rat adrenal cells replaced by LC from test for related peptides

Tragacanth (0532)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Tributyl acetyl citrate (1770)

Identification: comparison made using a CRS instead of a reference spectrum, in accordance with current policy.

Related substances: technical improvements have been added; the limits have been revised on the basis of batch data; specified impurity C and other detectable impurities D and E have been added.

Assay: heating for 3 h under reflux is necessary to achieve complete hydrolysis.

Trypsin (0694)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used.

Tryptophan (1272)

Related substances: 1,1'-ethylidenebistryptophan CRS is produced by evaporation. Preparation of reference solutions have been modified accordingly. A maximum value of 3.5 has been added for the symmetry factor.

Water for injections (0169)

Microbiological monitoring: the 5-day incubation time has been replaced by a more practical requirement of not less than 5 days; addition of criteria for growth promotion of the R2A medium used for microbiological monitoring; such criteria are routinely included for media in the Ph. Eur. to ensure suitability. Requirements similar to those stated in the harmonised chapter (2.6.12 and 2.6.13) are mentioned.

Conductivity: this section has already been revised for harmonisation with the USP draft; in view of changes to the USP, the Ph. Eur. monograph is revised again; the changes are also intended to clarify the text, which has been the subject of numerous enquiries from users; a tolerance of ± 2 °C for temperature measurement has also been added for harmonisation with the USP.

Heavy metals (Water for Injections in bulk): in view of the conductivity requirements, the test for heavy

metals is now superfluous (see G. Torres, A. Arsitio and C. Genovesi, Comparison of EP 'Heavy metals' test with USP 'Conductivity' test, Pharmaceutical Technology, January 2005, 80-81).

Oxidisable substances (Sterilised water for injections): the present requirement is too strict for containers with a volume less than 50 ml; although these containers may comply at release, containers that have been found to be suitable for pharmaceutical use are frequently non-compliant by the end of the shelf-life; a relaxed limit is included for these containers.

Ammonium (Sterilised water for injections): for the same reasons as stated for the test for Oxidisable substances, a relaxed limit (0.6 ppm) is included for containers with a volume less than 50 ml.

Heavy metals (Sterilised water for injections): the test for Water for injections in bulk is deleted, and since there is no possibility of contamination during the preparation of sterilised water for injections from water for injections in bulk, the test is also deleted at this stage.

Water, highly purified (1927)

Microbiological monitoring: the 5-day incubation time has been replaced by a more practical requirement of not less than 5 days; addition of criteria for growth promotion of the R2A medium used for microbiological monitoring; such criteria are routinely included for media in the Ph. Eur. to ensure suitability. Requirements similar to those stated in the harmonised chapter (2.6.12 and 2.6.13) are mentioned.

Conductivity: this section has already been revised for harmonisation with the USP draft; in view of changes to the USP, the Ph. Eur. monograph is revised again; the changes are also intended to clarify the text, which has been the subject of numerous enquiries from users; a tolerance of ± 2 °C for temperature measurement has also been added for harmonisation with the USP.

Heavy metals: in view of the conductivity requirements, the test for heavy metal is now superfluous (see G. Torres, A. Arsitio and C. Genovesi, Comparison of EP 'Heavy metals' test with USP 'Conductivity' test, Pharmaceutical Technology, January 2005, 80-81).

Water, purified (0008)

Microbiological monitoring: the 5-day incubation time has been replaced by a more practical requirement of not less than 5 days; addition of criteria for growth promotion of the R2A medium used for microbiological monitoring; such criteria are routinely included for media in the Ph. Eur. to ensure suitability. Requirements similar to those stated in the harmonised chapter (2.6.12 and 2.6.13) are mentioned.

Conductivity: this section has already been revised for harmonisation with the USP draft; in view of changes to the USP, the Ph. Eur. monograph is revised again; the changes are also intended to clarify the text, which has been the subject of numerous enquiries from users; a tolerance of ± 2 °C for temperature measurement has also been added for harmonisation with the USP.

Heavy metals (Purified water in bulk): the test has been kept because the high limit for conductivity would not allow a proper control of heavy metals in purified water. However, the possibility of waiving the test if purified water in bulk complies with the stricter requirement given for water for injections in bulk has been added, since it is known that many, perhaps most, water production systems in Europe produce water with

low conductivity. To avoid the loss of metals during the preparation of the test solution by reduction of the volume on a water-bath, it is requested to add 0.1 M nitric acid to the 3 solutions (test, reference, blank solutions).

Microbial contamination (Purified water in containers): editorial changes notably to take account of the new harmonised chapters on microbiological quality.

Wheat starch (0359)

Identification A: the crossed nicol prisms are replaced by orthogonally orientated polarising plates or prisms, used nowadays in practice; the identification section is harmonised and the change has been agreed within the PDG.

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. A test for Salmonella has been added because of possible infection via water rinse.

Xanthan gum (1277)

Microbial contamination: the implementation of the internationally harmonised chapters 2.6.12, 2.6.13 and 5.1.4 (supplement 5.6) required the revision of the acceptance criteria and the style used. Testing of *Escherichia coli* has been removed because irrelevant for a substances produced by fermentation.

Xylitol (1381)

Identification C: minor changes to the TLC in accordance with current policy.

Related substances/Assay: introduction of the use of a capillary column, which improves the sensitivity of the method and allows a better separation; improvement of the description of the method by introduction of a split ratio, a system suitability requirement and a disregard limit, and correction of the temperature gradient.

EDQM News

EDQM AND INDIAN AUTHORITIES TO WORK MORE CLOSELY ON DRUG QUALITY

The European Directorate for the Quality of Medicines & HealthCare (EDQM, Council of Europe), the Ministry of Health of India and the Indian Pharmacopoeia Commission (IPC) held a meeting in April this year to discuss how to strengthen their working relationship in order to improve the quality of medicines in Europe and India.

Dr Susanne Keitel, Director of the EDQM, and Dr Claude Coune (EDQM) met with the Honorable Dr Anbumani Ramadoss, Minister of Health & Family Welfare, Dr Surinder Singh (Drugs Controller General of India) and Dr G. N. Singh, the Secretary-cum-Scientific Director of the IPC, in New Delhi and at the IPC's headquarters in Ghaziabad.

"The EDQM is pleased to reinforce its partnership with the Indian authorities and the Indian Pharmacopoeia Commission and would welcome an application from India for observer status to the European Pharmacopoeia Commission" said Dr Keitel. In response, Dr Singh added "the Indian Pharmacopoeia Commission looks forward to a long-term relationship with the EDQM and the European Pharmacopoeia, one in which we can exchange our scientific expertise and work together on a variety of activities that will benefit all consumers of medicines in our respective countries".

Potential areas of collaboration identified include:

- elaboration of chemical and herbal monographs;
- development of joint inspections of manufacturing sites under the framework of the European Pharmacopoeia procedure of certification;
- promotion of common training activities in the pharmacopoeial field;
- scientific co-operation by inviting pharmaceutical scientists to the EDQM;
- facilitation of information exchange;
- observer status for the European Pharmacopoeia Commission to the Indian Pharmacopoeia Commission.

The EDQM and Indian authorities have worked closely together since 2002, when EDQM staff participated in a DIA conference organised in Goa on 25-27 October 2002. Since then, both authorities are in regular contact and have held several meetings to prepare the foundation for further co-operation.