

COMMENTS CONCERNING SOME REVISED/CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 6.6

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the November 2008 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

GENERAL TEXTS

2.2.31. Electrophoresis

This chapter has been revised to indicate its status within the context of pharmacopoeial harmonisation, a collaboration between the JP, the USP and the Ph. Eur. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

2.2.42. Density of solids

This chapter has been harmonised bilaterally between the USP and the Ph. Eur. The terminology has been reviewed to reflect the current practice in this field.

2.2.47. Capillary electrophoresis

2.2.54. Isoelectric focusing

2.2.55. Peptide mapping

2.2.56. Amino acid analysis

These chapters have been revised to indicate their status within the context of pharmacopoeial harmonisation, a collaboration between the JP, the USP and the Ph. Eur. A footnote has been included in the texts to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

2.4.29. Composition of fatty acids in oils rich in omega-3 acids

During the establishment of *EPA ethyl ester CRS 3* and *DHA ethyl ester CRS 3*, it appeared that each CRS contained a non-negligible amount of the other ethyl ester. Since this would interfere in the determination of the content of EPA, respectively DHA, it was necessary to prepare separate reference solutions containing *EPA ethyl ester CRS* or *DHA ethyl ester CRS*, instead of a mixture of both. The calculation formula was also adapted.

2.6.14. Bacterial endotoxins

The revision for this general chapter is the consequence of pharmacopoeial harmonisation. A number of clarifications have been included. For the calculation of the endotoxin limit, the maximum recommended concentration is no longer defined for a single hour period but for a bolus dose.

Test for bacterial endotoxins: guidelines. This section, which is not part of pharmacopoeial harmonisation, has been deleted from the chapter and included in part 5 of the European Pharmacopoeia.

2.6.17. Test for anticomplementary activity of immunoglobulin

Test for anticomplementarity activity. The adjustment of the immunoglobulin to pH 7 has been revised to be left up to the manufacturer, since it has been demonstrated that this requirement depends on the product characteristics. The choice must also be supported by validation data.

2.9.3. Dissolution test for solid dosage forms

Apparatus 4: the internal dimension of the tablet holder for the small cell (Figure 2.9.3.-6, bottom) was corrected (9.5 mm instead of 6.5 mm); a statement has been added on the need to characterise the dissolution test procedure as regards the rate and any pulsation of the pump.

2.9.7. Friability of uncoated tablets

2.9.26. Specific surface area by gas adsorption

These chapters have been revised to indicate their status within the context of pharmacopoeial harmonisation, a collaboration between the JP, the USP and the Ph. Eur. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

2.9.31. Particle size analysis by laser light diffraction

This text has been revised to reflect the text signed off by the 3 pharmacopoeias within the framework of pharmacopoeial harmonisation. Warnings have been added as regards the instrument location and the development of the method (see in particular the subsection Validation). The terminology used for the control of the instrument performance has been reviewed (calibration and qualification of the system).

2.9.36. Powder flow

2.9.37. Optical microscopy

2.9.38. Particle-size distribution estimation by analytical sieving

These chapters have been revised to indicate their status within the context of pharmacopoeial harmonisation, a collaboration between the JP, the USP and the Ph. Eur. A footnote has been included in the texts to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

5.2.2. Chicken flocks free from specified pathogens for the production and quality control of vaccines

Tests for freedom of antibodies to avian leucosis virus subtypes A, B and J. An enzyme immunoassay (EIA) was requested for establishment of an SPF flock and virus neutralisation (VN) was requested for routine testing (see Table 5.2.2.-1). To take into account recent progress of commercial detection kits, both methods (EIA and VN) can be requested at both stages (establishment of an SPF flock and routine testing of designated SPF flocks).

5.8 Pharmacopoeial Harmonisation

This chapter has been revised within the framework of pharmacopoeial harmonisation.

5.14. Gene transfer medicinal products for human use

2 new sections have been introduced that cover retroviridae-derived vectors and adeno-associated-virus vectors for human use. Minor modifications have been made to the already-published sections.

GENERAL MONOGRAPHS

Allergen products (1063)

The monograph has been extensively revised to take account of current requirements and techniques used in the field of allergen preparations, in particular, the following changes have been taken into account.

Definition: products used on a named-patient basis are covered.

Source materials: a more detailed description has been included; paragraphs have been added for hymenoptera venoms and food; the content of residual solvents, heavy metals and pesticides is determined on a number of batches according to an appropriate sampling plan; the text has been aligned with the draft EMEA Guideline on allergen products: production and quality issues (EMEA/CHMP/BWP/304831/2007).

Manufacturing process: a more detailed description has been included; the stages for the manufacturing process have been defined as source material, active substance and finished product; all other stages of the manufacturing process are considered as intermediates.

In-house reference preparation (IHRP): clarification has been made as to the use of in vivo or in vitro methods for the establishment of 1st and subsequent IHRP.

Water: if approved by the competent authority, the water content for oral lyophilisates may be higher than 5 per cent.

Sterility: the skin test preparations are not covered by the general monograph Parenteral preparations (0520); however, sterility is a reasonable requirement for these products.

Microbial contamination: a reference to chapter

5.1.4. *Microbial quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use* has been added for non-sterile allergen products.

Protein content: the range for protein content has been redefined. If the biological potency test can be performed, the protein content test is performed as a batch-to-batch consistency test.

Abnormal toxicity: to reduce the number of animal tests this test has been deleted, based on the following reasons:

- the test was included in the monograph for allergens obtained from moulds because it was considered as a higher risk, due to possible contamination by mycotoxins; no batch data demonstrating a higher risk could be found;
- from a statistical point of view, the low number of animals tested is very unlikely to reveal any toxic contamination.

A statement has been added in the production section saying that products obtained from moulds and intended for parenteral administration, if tested, would comply.

Antigen profile: the test has been deleted.

Total allergenic activity: the range for total allergenic activity has been narrowed to 50-150 per cent, because analysis of batch release data revealed that more than 90 per cent of batches of skin test allergens are within this range, indicating that it will be possible to adjust the activity of allergen products more precisely and the lower limit was kept in order to take account of the inevitable decline in activity of this type of biological product during storage.

Labelling: the name of the allergen product is stated.

VACCINES FOR HUMAN USE

Hepatitis A vaccine (inactivated, adsorbed) (1107)

Hepatitis A vaccine (inactivated, virosome) (1935)

Extraneous agents. The requirement has been deleted for the master seed lot. There is no added value to perform the test for both the master and the working seed lots. The change is in-line with other viral vaccines.

Pertussis vaccine (whole cell, adsorbed) (0161)

The monograph has undergone a general revision in order to take into account the recently approved WHO recommendations. Particularly, the title has been changed. Furthermore, the monograph is presented in the current format to be used for human vaccines.

VACCINES FOR VETERINARY USE

Clostridium novyi (type B) vaccine for veterinary use (0362)

Batch safety test. This vaccine was in the past intended for sheep only. Since this is not anymore the case, the

test has to be performed in the target species and not only in sheep. This is in line with the other monographs on Clostridium vaccines (0360, 0361, 0363 and 0364).

RADIOPHARMACEUTICAL PREPARATIONS

Iobenguane sulphate for radiopharmaceutical preparations (2351)

Loss on drying: addition of a test.

Bacterial endotoxins: addition of a test, following a recent agreement to include bacterial endotoxin tests in all

monographs of substances used for radiopharmaceutical preparations.

Impurity A: test previously entitled Related substances; modification in the preparation of the solutions in order to improve the solubility of the substance.

MONOGRAPHS

Almond oil, refined (1064)

Specific absorbance: the oil shows an absorption maximum at 270 nm which is the absorption maximum of conjugated trienes. A statement was added on the possible need to adapt the concentration of the test solution so that the absorbance lies in the range where the response of the apparatus is linear (0.5-1.5).

Water: the sample size has been reduced; to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil.

Composition of fatty acids: information on equivalent chain length has been deleted because it is already stated in chapter 2.4.22 and columns coated with polyethyleneglycol adipate are no longer used.

Labelling: the section has been deleted to follow the modifications made in the test for water.

Almond oil, virgin (0261)

Absorbance: the oil shows an absorption maximum at 270 nm which is the maximum absorbance of conjugated trienes.

Water: in order to harmonise the requirements included in the monographs on vegetable oils, a test for water content was added; this quality criterion is often requested by users to improve the microbiological quality of the final preparation. The microdetermination method (2.5.32), whose sensitivity is particularly adapted to low water contents was retained. A limit of maximum 0.1 per cent is appropriate for a non-hygroscopic oil. A phase separation occurs above 0.1 per cent.

Composition of fatty acids: information on equivalent chain length was deleted because it is already stated in chapter 2.4.22 and columns coated with polyethyleneglycol adipate are no longer used.

Amikacin (1289)**Amikacin sulphate (1290)**

Related substances: amikacin impurity A CRS is no longer available and has been replaced by amikacin for system suitability CRS, which consists of amikacin containing a small amount of impurity A; the relative retention of impurity A is now specified and the quantification of impurity A is no longer achieved by comparison with impurity A, but rather by comparison with the main substance.

Arachis oil, refined (0263)

Composition of fatty acids: information on equivalent chain length was deleted because it is already stated in chapter 2.4.22 and columns coated with polyethyleneglycol adipate are no longer used.

Water: in order to harmonise the requirements included in the monographs on vegetable oils, the microdetermination method (2.5.32) for water, whose sensitivity is particularly adapted to low water contents, has been retained instead of the semi-microdetermination method (2.5.12). A limit of maximum 0.1 per cent is appropriate as a general quality criterion regardless of the use of the oil. The sample size has been reduced.

Labelling: the section has been deleted to follow the modifications made in the test for water.

Artichoke leaf (1866)

Identification C: the composition of the mobile phase for the TLC has been adapted to avoid separation into 2 phases.

Artichoke leaf dry extract (2389)

Identification: the composition of the mobile phase has been adapted to avoid separation into 2 phases.

Borage (starflower) oil, refined (2105)

Composition of the fatty acids: the equivalent chain length has been deleted because this information is already available in chapter 2.4.22.

Water: the sample size has been reduced; to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil.

Budesonide (1075)

Definition: lower content limit reduced.

Related substances: LC procedure revised and list of impurities updated to reflect results from current market batches.

Methanol: test removed since the limit for methanol is covered by the general monograph *Substances for pharmaceutical use (2034)* and general chapter 5.4. *Residual solvents.*

Epimer A, Assay: the LC method approved for the related substances test is also applied for the test for epimer A and for the assay.

Cimetidine (0756)**Cimetidine hydrochloride (1500)**

Identification: the TLC has been simplified so that there is only 1 development of the plates; the test for colour reaction has been deleted.

Related substances: the TLC has been replaced by an LC which allows the control of related substances from different routes of synthesis.

Storage: storage in an airtight container is not necessary.

Clobetasone butyrate (1090)

Identification: tests B and C deleted since IR (without information about sample preparation) considered to be sufficient for identification.

Specific optical rotation: solvent substituted to avoid use of dioxan and limits adjusted accordingly.

Related substances: LC method modified to widen spectrum of detectable impurities.

Impurities: list updated based on current batch data.

Coconut oil, refined (1410)

Water: in order to harmonise the requirements included in the monographs on vegetable oils, a test for water content has been added; this quality criterion is often requested by users to improve the microbiological quality of the final preparation. The microdetermination method (2.5.32), whose sensitivity is particularly adapted to low water contents, has been retained. A limit of maximum 0.1 per cent is appropriate for a non-hygroscopic oil. A phase separation occurs above 0.1 per cent.

Dandelion herb with root (1851)

Identification B: illustrations of powdered herbal drug introduced.

Dextropropoxyphene hydrochloride (0713)

Definition: upper limit for content raised to 101.5 per cent.

Identification: 2nd identification deleted as not of practical relevance for this substance.

Related substances: LC modified to allow better quantification of isopropoxyphene and to cover 3 additional impurities.

Heavy metals: test deleted as not of practical relevance for this substance.

Evening primrose oil, refined (2104)

Composition of fatty acids: information on equivalent chain length has been deleted because it is already stated in chapter 2.4.22.

Water: the sample size has been reduced; to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil.

Ferrous sulphate heptahydrate (0083)

Solution S: a new preparation has been described, since the solution is used in the tests by atomic absorption spectrometry (AAS).

Appearance of solution: unnecessary, the test has been deleted.

pH: the volume of the solution has been increased.

Chlorides, Ferric ions: limits have been adjusted based on current batch data.

Chromium, Copper, Nickel: individual determination by AAS instead of a test for heavy metals, which has been deleted.

Manganese, Zinc: determination by AAS instead of current methods.

Gemfibrozil (1694)

Related substances: the correction factors of impurities D, H and I have been corrected.

Glipizide (0906)

Related substances: the test has been revised to introduce a new single LC method and to control 4 additional impurities (impurities F, G, H and I).

Impurity C: the test has been deleted because impurity C is covered by the new test for related substances.

Goldenseal rhizome (1831)

Since hydrastine hydrochloride is not stable in methanolic solutions, the reference solutions in identification C and in the assay should be prepared immediately before use.

Identification C: conditions for HPTLC have been added.

Assay: the dilution of the test solution has been changed to have similar amounts of hydrastine/berberine in the test and reference solutions; consequently the calculation formula has been adapted.

Hydrastine hydrochloride R and *berberine chloride R* have been replaced by *hydrastine hydrochloride CRS* and *berberine chloride CRS*.

Guar (1218)

Functionality-related characteristics: this section has been added. Guar is a polysaccharide producing colloidal solutions with cold water. It has traditionally been used as viscosity-increasing agent and tablet binder. A cross-reference to the test for apparent viscosity has been included under FRCs, this test being useful to assess both the quality, in terms of different grades, and the functionality of this excipient.

Guar galactomannan (0908)

Functionality-related characteristics: this section has been added. Guar galactomannan is purified guar. It has been reported in the literature that it has a higher viscosity and a faster rate of hydration than guar, resulting in improved tablet properties. It is used as viscosity-increasing agent and binder. A cross-reference to the test for apparent viscosity has been included under FRCs, this test being useful to assess both the quality, in terms of different grades, and the functionality of this excipient.

Hawthorn leaf and flower (1432)

Assay: to avoid the use of different qualities of acetic acid, glacial acetic acid has been replaced by anhydrous acetic acid.

Hawthorn leaf and flower dry extract (1865)

Assay: to avoid the use of different qualities of acetic acid, glacial acetic acid has been replaced by anhydrous acetic acid.

Human albumin solution (0255)

Pyrogens. The European Pharmacopoeia Commission has a policy of regular review of animal tests prescribed in monographs with a view to their replacement by in vitro methods wherever possible, in accordance with the European Convention on the Use of Animals for Experimental and Other Scientific Purposes and with EU Directive 86/609/EC. The revised monograph introduces a provision for use of an in vitro method as a preferred alternative to the pyrogen test in rabbits. Acceptance criteria for application of the bacterial endotoxin test (2.6.14) (BET) are included, since this is the in vitro test currently applied to plasma products. The use of the BET instead of the pyrogen test is reliable where the pyrogenic substances present are endotoxins. The comparison of results of the 2 tests on thousands of production batches of plasma products confirmed that both tests detected the same batches as contaminated, i.e. batches containing non-endotoxin pyrogenic substances have not been encountered.

Use of an *in vitro* test is subject to regulatory approval following submission of data demonstrating suitable control of the manufacturing process. The Biologicals Working Party of the Committee for Human Medicinal Products of the European Medicines Agency is currently developing a guideline on the regulatory requirements for a change to bacterial endotoxin testing. This guideline will facilitate the application of the provisions of the revised monograph.

The acceptance criteria take account of: the threshold pyrogenic dose (5 IU/kg) as recommended in chapter 2.6.14; the maximum recommended dose of the product; feasibility in light of experience with current production; the BET acceptance criteria approved by the US FDA for replacement of the pyrogen test.

Human coagulation factor VIII (0275)

Pyrogens. The European Pharmacopoeia Commission has a policy of regular review of animal tests prescribed in monographs with a view to their replacement by in vitro methods wherever possible, in accordance with the European Convention on the Use of Animals for Experimental and Other Scientific Purposes and with EU Directive 86/609/EC. The revised monograph introduces a provision for use of an in vitro method as a preferred

alternative to the pyrogen test in rabbits. Acceptance criteria for application of the bacterial endotoxin test (2.6.14) (BET) are included, since this is the *in vitro* test currently applied to plasma products. The use of the BET instead of the pyrogen test is reliable where the pyrogenic substances present are endotoxins. The comparison of results of the 2 tests on thousands of production batches of plasma products confirmed that both tests detected the same batches as contaminated, i.e. batches containing non-endotoxin pyrogenic substances have not been encountered.

Use of an *in vitro* test is subject to regulatory approval following submission of data demonstrating suitable control of the manufacturing process. The Biologicals Working Party of the Committee for Human Medicinal Products of the European Medicines Agency is currently developing a guideline on the regulatory requirements for a change to bacterial endotoxin testing. This guideline will facilitate the application of the provisions of the revised monograph.

The acceptance criteria take account of: the threshold pyrogenic dose (5 IU/kg) as recommended in chapter 2.6.14; the maximum recommended dose of the product (excluding the very high doses of factor VIII used in a small number of patients); feasibility in light of experience with current production; the BET acceptance criteria approved by the US FDA for replacement of the pyrogen test.

Human normal immunoglobulin (0338)

Human normal immunoglobulin for intravenous administration (0918)

Pyrogens. The European Pharmacopoeia Commission has a policy of regular review of animal tests prescribed in monographs with a view to their replacement by *in vitro* methods wherever possible, in accordance with the European Convention on the Use of Animals for Experimental and Other Scientific Purposes and with EU Directive 86/609/EC. The revised monograph introduces a provision for use of an *in vitro* method as a preferred alternative to the pyrogen test in rabbits. Acceptance criteria for application of the bacterial endotoxin test (2.6.14) (BET) are included, since this is the *in vitro* test currently applied to plasma products. The use of the BET instead of the pyrogen test is reliable where the pyrogenic substances present are endotoxins. The comparison of results of the 2 tests on thousands of production batches of plasma products confirmed that both tests detected the same batches as contaminated, i.e. batches containing non-endotoxin pyrogenic substances have not been encountered.

Use of an *in vitro* test is subject to regulatory approval following submission of data demonstrating suitable control of the manufacturing process. The Biologicals Working Party of the Committee for Human Medicinal Products of the European Medicines Agency is currently developing a guideline on the regulatory requirements for a change to bacterial endotoxin testing. This guideline will facilitate the application of the provisions of the revised monograph.

The acceptance criteria take account of: the threshold pyrogenic dose (5 IU/kg) as recommended in chapter 2.6.14; the maximum recommended dose of the product; feasibility in light of experience with current production; the BET acceptance criteria approved by the US FDA for replacement of the pyrogen test.

Lansoprazole (2219)

Water: the coulometric determination has been improved by applying the evaporation technique, for which the optimal conditions (temperature, weight) are now given.

Linseed oil, virgin (1908)

Water: the sample size has been reduced.

Composition of fatty acids: information on equivalent chain length was deleted because it is already stated in chapter 2.4.22 and columns coated with polyethyleneglycol adipate are no longer used.

Liquorice root (0277)

Ochratoxin A: a test has been introduced, the limit being in line with that proposed in the draft Commission Regulation (EC), document SANCO/00875/2007-rev 2.

Loratadine (2124)

Related substances: the correction factor of impurity E has been corrected.

Lovastatin (1538)

Identification B: sample preparation deleted because superfluous.

Appearance of solution: test deleted because substance not used in preparations for parenteral use and no information available to justify keeping the test.

Related substances: test modified to increase concentration of test solution used in assay and provide better quantification of impurities; acceptance criterion for unspecified impurities added.

Impurity E: test added for specified impurity E, which cannot be detected by the test for related substances.

Heavy metals: method C replaced by method F in accordance with current policy.

Impurities: addition of specified impurity E.

Maize oil, refined (1342)

Water: the sample size has been reduced; to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil. No specific solvent being required for this oil, the corresponding statement has been deleted.

Mefenamic acid (1240)

Definition: upper content limit widened to 101.0 per cent to give symmetrical limits in accordance with Ph. Eur. policy.

Nortriptyline hydrochloride (0941)

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

Impurities: list updated based on current batch data.

Olive oil, refined (1456)

Water: the sample size has been reduced; to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil; no specific solvent being required for this oil, the corresponding statement has been deleted.

Olive oil, virgin (0518)

Characters: the statement on characteristic odour has been deleted.

Water: in order to harmonise the requirements included in the monographs on vegetable oils, a test was added; this quality criterion is often requested by users to improve the microbiological quality of the final preparation. The microdetermination method

(2.5.32), whose sensitivity is particularly adapted to low water contents, was retained. A limit of 0.1 per cent is appropriate for a non-hygroscopic oil. A phase separation occurs above 0.1 per cent.

Oxygen (0417)

Appearance: the character odourless has been deleted.

Production: the manufacturing method is now stated.

Identification: identification tests A and B are not specific for medicinal oxygen; to allow the differentiation from lower grades of oxygen, the assay needs to be performed.

Storage: a more precise requirement is stated for the use of grease and oils.

Peppermint leaf (0406)

Identification B: the monograph has been republished to introduce the illustration of the powdered herbal drug.

Phenazone (0421)

Definition: upper limit of content has been increased to 101.0 per cent in accordance with current policy.

Identification: sample preparation has been deleted as it is superfluous.

Related substances: in the framework of a special revision programme, an LC test has been included; limits are based on current batch data and on the maximum daily dose.

Impurities: section has been introduced showing impurity A, controlled by LC.

Potassium clavulanate (1140)

Absorbance: the test has been renamed, since it also covers the polymeric impurities; the limit has not been changed.

Related substances: the previous transparency statement and impurity limits have been updated based on recent batch data from the market. The list of specified impurities detected by LC has therefore been reduced to E and G; the limit for 'any other impurity' has been tightened to 0.2 per cent; and a system suitability CRS has been introduced.

Impurities: has been deleted, since in practice this aliphatic amine is not used as a starting material for the synthesis of potassium clavulanate in Europe.

Potassium clavulanate, diluted (1653)

Absorbance: the test has been renamed since it also covers the polymeric impurities; the limit has not been changed.

Related substances: the previous transparency statement and impurity limits have been updated based on recent batch data from the market. The list of specified impurities detected by LC has therefore been reduced to E and G; the limit for 'any other impurity' has been tightened to 0.2 per cent; and a system suitability CRS has been introduced.

Pravastatin sodium (2059)

Related substances: additional specified impurity G added.

Pyridoxine hydrochloride (0245)

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

Rapeseed oil, refined (1369)

Water: in order to harmonise the requirements included in the monographs on vegetable oils, a test for water

content has been added; this quality criterion is often requested by users to improve the microbiological quality of the final preparation. The microdetermination method (2.5.32), whose sensitivity is particularly adapted to low water contents has been retained. A limit of maximum 0.1 per cent is appropriate for a non-hygroscopic oil. A phase separation occurs above 0.1 per cent.

Safflower oil, refined (2088)

Composition of fatty acids: information on equivalent chain length has been deleted because it is already stated in chapter 2.4.22 and columns coated with polyethyleneglycol adipate are no longer used.

Water: the sample size has been reduced; to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil.

Sesame oil, refined (0433)

Water: in order to harmonise the requirements included in the monographs on vegetable oils, the microdetermination method (2.5.32) for water, whose sensitivity is particularly adapted to low water contents has been retained, instead of the semi-microdetermination method (2.5.12). A limit of maximum 0.1 per cent is appropriate as a general quality criterion whatever the use of the oil. The sample size has been reduced.

Sodium alginate (0625)

Functionality-related characteristics: this section has been added. Sodium alginate is mainly used as viscosity-increasing agent. In solid dosage forms it is also used as binder. A test for apparent viscosity has therefore been added.

Soya-bean oil, refined (1473)

Water: to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil; no specific solvent being required for this oil, the corresponding statement has been deleted.

Starch, pregelatinised (1267)

Functionality-related characteristics: this section has been added. Pregelatinised starch is used as filler, binder or disintegrant in tablets and in hard capsules. Particle-size distribution by laser diffraction and powder flow are important FRCs. The degree of pregelatinisation is also a relevant criterion for these uses but no direct method exists: it is indirectly assessed by determining the percentage content of matters soluble in cold water.

Sunflower oil, refined (1371)

Water: in order to harmonise the requirements included in the monographs on vegetable oils, a test for water content has been added; this quality criterion is often requested by users to improve the microbiological quality of the final preparation. The microdetermination method (2.5.32), whose sensitivity is particularly adapted to low water contents, has been retained. A limit of maximum 0.1 per cent is appropriate for a non-hygroscopic oil. A phase separation occurs above 0.1 per cent.

Terbinafine hydrochloride (1734)

Related substances: the LC test has been revised to appropriately control impurities E and F.

Impurities: specified impurity E and unspecified impurity F have been added.

Theophylline-ethylenediamine, anhydrous (0300)

Title: addition of 'anhydrous' in the title (there is a

monograph on *Theophylline-ethylenediamine hydrate* (0301)).

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

Related substances: TLC replaced by LC in accordance with current policy as part of a special revision programme; proposal harmonised with the current monograph *Theophylline* (0299).

Heavy metals: method C replaced by an alternative method in accordance with current policy.

Impurities: section introduced showing impurities controlled by the LC.

Theophylline-ethylenediamine hydrate (0301)

Formulae: graphic formula introduced.

Related substances: TLC replaced by LC in accordance with current policy as part of a special revision programme; test harmonised with the current monograph for *Theophylline* (0299).

Heavy metals: method C replaced by an alternative method in accordance with current policy.

Impurities: section introduced showing impurities controlled by the LC.

Triglycerides, medium-chain (0868)

Definition: medium-chain triglycerides are not directly obtained from the oil extracted from the endosperm of *Cocos nucifera* L. or *Elaeis guineensis* Jacq. The fatty acids are derived from the oil and further esterified with glycerol. The definition has been revised to better define this process.

Wheat-germ oil, refined (1379)

Water: the sample size has been reduced; to harmonise with the other vegetable oils, the test is applicable regardless of the use of the oil. No specific solvent being required for this oil, the corresponding statement has been deleted.

Wheat-germ oil, virgin (1480)

Water: the sample size has been reduced. No specific solvent being required for this oil, the corresponding statement has been deleted.

Zinc sulphate monohydrate (2159)

pH: the acceptable range has been widened to 4.0 to 5.6.

TECHNICAL GUIDE FOR THE ELABORATION OF MONOGRAPHS

available as a free download on the EDQM website
and as a cumulative printed version

The Technical Guide for the Elaboration of Monographs (2005) describes the scientific approach used for the elaboration of monographs and the establishment of specifications of the European Pharmacopoeia. The guide also describes how to elaborate scientifically the various sections that must be included in each monograph, for example definition, characters, the physical and chemical reactions constituting the identification section, purity tests, assay methods and storage conditions. It is continually being updated.

Specific guides are also available for:

- Monographs on vaccines and other immunological human medicinal products (2008)
- Monographs on fatty oils and derivatives (2007)
- Monographs on herbal drugs and herbal drug preparations (2007)
- Monographs on synthetic peptides and recombinant DNA proteins (2006)
- The graphic representation and nomenclature of chemical formulae in the European Pharmacopoeia (2006)

Available in English and French as a free download from the EDQM website (<http://www.edqm.eu>).

Printed cumulative version: for ordering, please consult our website <https://www.edqm.eu/store>