

## Comments Concerning Revised Texts Published in the 7<sup>th</sup> Edition

Here follows information concerning technical modifications to revised texts adopted by the European Pharmacopoeia Commission at the December 2009 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

### GENERAL TEXTS

#### 2.5.24. Carbon dioxide in gases

Definition revised as regards absorption of light by gases.

#### 2.5.25. Carbon monoxide in gases

Method II revised as regards absorption of light by gases.

#### 2.5.35. Nitrous oxide in gases

General chapter revised because infrared analysers with 2 infrared sources, such as those currently described in the Ph. Eur., are no longer commercialised. The chapters on carbon monoxide and carbon dioxide in gases (2.5.25 and 2.5.24) have already been similarly revised (Supplement 6.3).

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

Comments received following publication in Pharmeuropa have led to a reconsideration of the feasibility of broadening the scope to cover cell substrates for the production of biological products for human use. The revised text therefore covers only viral vaccines for human use, but takes account of novel production substrates based on insect cell systems.

**Spiroplasmas (Virus seed lot):** requirement added that virus seed lots derived from insect cell systems be shown to be free of spiroplasmas.

**Test in cell culture for other extraneous agents (Virus seed lot and virus harvests):** clarification of the section; testing on a 3<sup>rd</sup> cell system is required if the virus is grown in a cell system other than simian or human.

**Avian viruses (Virus seed lot and virus harvests):** clarified that the test needs to be carried out for virus seed lot propagated in avian tissues and for virus harvest propagated in primary avian tissues.

**Insect viruses (Virus seed lot and virus harvests):** new section to deal with testing of seeds from insect cells for extraneous agents; the principle of the testing is that cells from at least one cell line that is different from that used in production and permissible to insect viruses, and that allows detection of human arboviruses, is used.

#### Tests in cell cultures for other extraneous agents

**(Production cell culture: control cells):** new paragraph introduced to deal with testing of control cells from insect cell production systems; again, at least one cell line is tested to detect human arboviruses and insect-specific viruses.

#### 2.6.27. Microbiological control of cellular products

*Aspergillus niger* replaced by *Aspergillus brasiliensis* as a consequence of the renaming of strains ATCC 16404 and ATCC 9642. This has no impact on the characterisation of the micro-organism or on the performance of the test.

#### 2.7.14. Assay of hepatitis A vaccine

**In vitro assay: hepatitis A vaccine (inactivated, non-adsorbed) BRP** has been introduced as a suitable reference preparation. The establishment of the hepatitis A vaccine (inactivated, non-adsorbed) BRP batch 1 has been carried out as an extensive project in the Biological Standardisation Programme of the EDQM and was supported by the Council

of Europe and the European Commission. The report of the project has been published in Pharmeuropa Bio & Scientific Notes 2010-1.

#### 5.1.2. Biological indicators of sterilisation

Names of micro-organisms have been changed to be in line with current taxonomic nomenclature. Some requirements have been aligned with EN ISO 11138.

#### 5.1.3. Efficacy of antimicrobial preservation

*Aspergillus niger* replaced by *Aspergillus brasiliensis* as a consequence of the renaming of strains ATCC 16404 and ATCC 9642. This has no impact on the characterisation of the micro-organism or on the performance of the test.

**Acceptance criteria:** titles of Tables 5.1.3.-1/2/3 clarified to take into account the specific pharmaceutical preparations that may contain antimicrobial preservatives; this will help users assign specific criteria for these preparations.

**'No increase' criterion:** it has been clarified that the log reduction for 'no increase' is calculated compared to the previous reading.

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

Black diamonds added to indicate that the Ph. Eur. special provision and the reference made to chapter 5.1.8 are local requirements; in the previous revision they had inadvertently been left out. Further information can be found in chapter 5.8. *Pharmacopoeial harmonisation.*

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

Comments received following publication in Pharmeuropa have led to a reconsideration of the feasibility of broadening the scope to cover cell substrates for the production of biological products for human use. The revised text therefore covers only vaccines for human use, but takes account of novel production substrates based on insect cell systems.

**Tumorigenicity:** testing strategy modified. The current strategy is based on *in vitro* testing followed by *in vivo* testing if the *in vitro* test is negative or not clearly positive. However, it has been shown in several cases that there is little correlation between the *in vitro* and *in vivo* tests. Moreover, tumorigenicity is defined as the process by which immortalised cells form tumours when inoculated into animals. Since the *in vitro* tests are not able to predict accurately the tumorigenic phenotype of cell lines, it has been decided to keep them for characterisation purposes only. This modification is in line with the on-going revision of the WHO guideline on cell substrates (TRS 878).

**Morphology:** text brought in line with Table 5.2.3.-1.

**Spiroplasmas (insect cell lines):** new section introducing the requirement that cell banks from insect cell production systems be shown to be free of spiroplasmas.

**Electron microscopy (insect cell lines):** new section to deal with the lack of a general test for viruses, such as those outlined in chapter 2.6.16. *Tests for extraneous agents*

*in viral vaccines for human use*; in this case, electron microscopy is used as a general test for identifying viruses that may replicate without causing cytopathic effects in insect cells.

**Co-cultivation:** additions made to this section to take account of insect cells used in production. The principle of the addition is that 3 cell lines are used: one human, one simian and one cell line that is different from that used in production, is permissible to insect viruses and allows detection of human arboviruses. Changes are also made to allow for testing of intact cells and/or disrupted cells since testing for intact cells may not be possible when cells in suspension are used for the production of a vaccine. In addition, changes are made to allow for testing by

haemadsorption as well as haemagglutination (alignment with the on-going revision of the WHO guideline on cell substrates, TRS 878).

**Specific tests for contamination:** additional section to clarify that which was previously presented in Table 5.2.3.-1. The test takes account of the history of the cells and the host from which they were derived. Allows for NAT testing (2.6.21) or the use of serological tests. Other changes have been made to clarify and harmonise the text and Table 5.2.3.-1.

#### 5.8. Pharmacopoeial harmonisation

The sections 2.2.47, 2.2.54, 2.2.55, 2.4.14 and 5.1.4 have been revised within the framework of pharmacopoeial harmonisation.

## VACCINES FOR HUMAN USE

### Measles, mumps, rubella and varicella vaccine (live) (2442) Varicella vaccine (live) (0648)

**Assay.** *Varicella vaccine (live) BRP* has been introduced as a suitable reference preparation. The establishment of the *varicella vaccine (live) BRP* batch 1 has been carried out

as an extensive project in the Biological Standardisation Programme of the EDQM and was supported by the Council of Europe and the European Commission. The report of the project is available in *Pharmeuropa Bio & Scientific Notes* 2009-1.

## RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

### Tetra-*O*-acetyl-mannose triflate for radiopharmaceutical preparations (2294)

**Related substances:** concentration of the test solution has been increased to improve sensitivity.

## HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

### Agrimony (1587)

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

### Angelica root (1857)

**Identification B:** the illustration of the powdered herbal drug has been introduced.

### Artichoke leaf (1866)

### Butcher's broom (1847)

### Calendula flower (1297)

### Capsicum (1859)

### Cinchona bark (0174)

### Dandelion root (1852)

### Devil's claw root (1095)

### Ginger (1522)

### Ginkgo leaf (1828)

### Goldenseal rhizome (1831)

### Hamamelis leaf (0909)

### Hop strobile (1222)

**Identification B:** the legend for the illustration of the powdered herbal drug has been integrated into the text of Identification B.

### Liquorice ethanolic liquid extract, standardised (1536)

**Ochratoxin A:** the test has been introduced.

### Mallow flower (1541)

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

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

### Melissa leaf (1447)

### Mullein flower (1853)

**Identification B:** the legend for the illustration of the powdered herbal drug has been integrated into the text of Identification B.

### Nettle leaf (1897)

**Identification B:** illustration of powdered herbal drug introduced.

**Identification C:** HPTLC conditions added.

**Assay:** method simplified using an external standard.

### Oregano (1880)

### Peppermint leaf (0406)

### Red poppy petals (1881)

**Identification B:** the legend for the illustration of the powdered herbal drug has been integrated into the text of Identification B.

## HOMOEOPATHIC PREPARATIONS

### Homoeopathic preparations (1038)

The general monograph has been revised to establish a link between manufacturing methods and the preparation of dosage forms and to state more precisely which methods are covered by these provisions.

### Methods of preparation of homoeopathic stocks and potentiation (2371)

The general monograph has been revised to introduce new homoeopathic manufacturing methods for liquid dilutions (including liquid dilutions of triturations), triturations, co-potentiations and glycerol macerates. All manufacturing methods have been reorganised and renumbered using a

more flexible system, which classifies methods according to the kind of preparation. Where a method originates from a national pharmacopoeia, this is indicated. Furthermore, where a method has been adapted from the German Homoeopathic Pharmacopoeia (Homöopathisches Arzneibuch; HAB), the equivalence with the HAB method numbers and titles is given for convenience. Where manufacturing practices currently in use in Europe were not described in a pharmacopoeia, new methods covering these practices have been elaborated; this concerns methods 3.1.3, 3.2.3, 4.2.2, 5.1.4 and 5.1.5. A table giving the correlation between the former and new numbering can be found in the Knowledge database.

## MONOGRAPHS

### Acetylsalicylic acid (0309)

**Related substances:** paragraph for identification of impurity C and relative retentions of specified impurities introduced; explicit acceptance criterion for unspecified impurities introduced; disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose > 2 g/day).  
**Impurities:** impurities A, B, C, D, E and F now listed as specified impurities.

### Aciclovir (0968)

**Related substances:** TLC and LC replaced by single LC; limit for unspecified impurities and disregard limit lowered to 0.05 per cent and 0.03 per cent respectively.  
**Impurities:** impurities A, B, C, F and G and new impurities I, J, K, N, O and P now listed as specified impurities; new impurities L and M listed as other detectable impurities; impurities D, E and H deleted since never found in production batches.

### Aluminium oxide, hydrated (0311)

**Functionality-related characteristics:** section added, with the following FRCs for hydrated aluminium oxide used as adsorbent: particle-size distribution by laser diffraction (particle size would not allow analytical sieving); specific surface area.

### Ambroxol hydrochloride (1489)

**Related substances:** information on identification and relative retention of impurity B introduced; wording of text aligned with general policy; disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose ≤ 2 g/day).  
**Impurities:** impurities A, B, C, D and E now listed as other detectable impurities.

### Aminoglutethimide (1291)

**Identification:** description of sample preparation deleted in accordance with current policy.  
**Related substances:** paragraph for identification of impurity A and explicit acceptance criterion for unspecified impurities introduced.

### Aprotinin (0580)

#### Aprotinin concentrated solution (0579)

**Production.** This monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and the presentation of this information. An editorial modification has been made to the statement concerning the health of the animals used for the preparation of aprotinin to align it with that of similar monographs.

**Pyroglutamyl-aptinin and related compounds.** Further to the establishment of *aprotinin for system suitability CRS* batch 1, the preparation of the reference solution has been amended in line with the indications provided in the leaflet. The gradient has been presented according to the general policy.

### Ascorbic acid (0253)

**Test for impurity E:** test amended to allow measurement of the neutrality of the solutions using either a pH meter or universal indicator paper.

**Related substances:** impurities C and D, determined by external standards, are excluded from the calculation of the total.

**Copper, Iron:** precision of limits modified in accordance with general policy.

### Azithromycin (1649)

**Related substances:** impurity G correction factor introduced and limit modified.

### Benazepril hydrochloride (2388)

**Characters:** statement on hygroscopicity added.

**Loss on drying:** limit increased based on additional batch data.

**Storage:** section changed due to hygroscopicity of substance.

### Buflomedil hydrochloride (1398)

**Identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** paragraph for identification of impurities introduced; relative retentions of impurities introduced; explicit acceptance criterion for unspecified impurities introduced.

**Impurities:** impurities A, B and C now listed as specified impurities.

### Calcium acetate, anhydrous (2128)

**Appearance of solution, fluorides, iron:** tests added.

**Magnesium and alkali metals:** test deleted.

**Arsenic:** limit increased to 3 ppm.

**Aluminium, Iron, Potassium, Sodium, Strontium:** tests restricted for specific uses.

**Barium, Magnesium, Potassium, Sodium, Strontium:** precision of limits modified in accordance with general policy.

**Heavy metals:** limit decreased to 10 ppm.

**Assay:** method replaced.

### Captopril (1079)

**Solubility:** solubility in water corrected.

**Identification:** addition of cross-reference to test for specific optical rotation.

**Related substances:** previous LC replaced by gradient LC allowing control of additional impurities.

**Impurity F:** test by GC added to control *epi*-captopril impurity.

**Storage:** section deleted since captopril is not hygroscopic.

**Impurities:** impurities A to F listed as specified impurities, impurities G, H, I, J, L, M, N and O listed as other detectable impurities.

#### **Carrageenan (2138)**

**Apparent viscosity:** a temperature of 75 °C was previously stated for the test. This is below the melting/dissolution temperature of carrageenans. The dispersion must first be heated to 80 °C before measuring the viscosity at 75 °C. Under such conditions, gelation of a 15 g/L solution will not occur and will therefore not interfere with the test.

#### **Chlorocresol (0384)**

**Related substances:** explicit acceptance criterion for unspecified impurities introduced; description of disregard limit aligned with current policy.

#### **Chymotrypsin (0476)**

**Trypsin:** 1/5 of previous buffer concentration sufficient, so volume of *tris(hydroxymethyl)aminomethane buffer solution pH 8.1 R* reduced to 0.01 mL.

#### **Cladribine (2174)**

**Solution S:** the description of the solution has been moved to the test for appearance of solution.

**pH:** the test has been deleted.

**Related substances:** the gradient has been presented according to the general policy; it has been added that the chromatogram obtained with reference solution (f) is used for identification of impurities.

**Labelling:** the section has been added where the substance is used in the manufacture of parenteral preparations.

#### **Clebopride malate (1303)**

**Identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** system suitability requirement and wording of test aligned with current policy; disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose ≤ 2 g/day).

**Impurities:** impurities A to C now listed as other detectable impurities.

#### **Codeine phosphate hemihydrate (0074)**

**Related substances:** impurities B and E now to be determined as a sum because separation is difficult to achieve.

#### **Danaparoid sodium (2090)**

**Definition and Production:** this monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and its presentation. The statement relative to the origin of the substance has been moved under Definition accordingly and a paragraph has been added regarding the health of the animals used for the preparation of danaparoid sodium.

#### **Fish oil, rich in omega-3 acids (1912)**

**Definition:** changes have been made to harmonise with monographs on similar products. In addition, a second type of fish oil is described: fish oil obtained from the genera *Thunnus* and *Sarda*. The corresponding quality is reflected in the monograph by different limits (assay, absorbance, anisidine value, peroxide value). Type II fish oil is used in baby food for premature babies and infants.

**Anisidine value:** cross-reference to the general

chapter 2.5.36 has been added. A limit of 15.0 is included for type II oil.

**Oligomers:** a differential refractometer is used for detection. Such detectors differ in sensitivity. In addition, small variations in temperature and flow rate may reduce the signal-to-noise ratio. It is therefore stated to inject a test solution that is 5 times more concentrated.

**Labelling:** type of fish oil (type I or II) is indicated.

#### **Flucytosine (0766)**

**Content:** lower limit tightened based on current batch results and according to Technical guide instructions.

**Identification B:** TLC test formerly used for both identification and related substances is now only described for identification and has been slightly modified.

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

**Fluorides:** wording of test revised to refer to general chapter 2.2.36. *Potentiometric determination of ionic concentration using ion-selective electrodes*.

**Impurities:** section introduced showing impurities controlled by LC test.

#### **Fluoxetine hydrochloride (1104)**

**Identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** paragraph for identification of impurities introduced; peak-to-valley ratio modified to be in line with definition in general chapter 2.2.46. *Chromatographic separation techniques*.

#### **Fluspirilene (1723)**

**Identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** wording of test aligned with general policy.

#### **Fosfomycin calcium (1328)**

**Identification:** replacement of IR spectrum by CRS.

#### **Fosinopril sodium (1751)**

**Related substances:** relative retentions of impurities I and K have been corrected in method A. In the test for impurities C and D, the system suitability criterion has been modified and *fosinopril impurity C CRS* and *fosinopril impurity D CRS* are injected in separate solutions to allow a suitable quantification of each of them.

**Heavy metals:** solvent changed.

#### **Ganciclovir (1752)**

**Water:** additional information introduced due to limited solubility of substance in reagent.

#### **Glycerol monocaprylocaprate (2392)**

**Assay:** calculations clarified.

#### **Gonadotrophin, chorionic (0498)**

**Definition and Production:** the monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and its presentation. The information relative to the origin of the substance has been moved to Definition accordingly.

#### **Haemodialysis, solutions for (0128)**

**Aluminium:** the way the pH is adjusted is stated.

**Sodium:** this monograph is revised by analogy with the revision for the monograph *Solutions for haemofiltration and haemodiafiltration (0861)*. Sodium emits as a doublet at 589.0 nm and 589.6 nm. Both wavelengths are therefore mentioned.

#### **Haemofiltration and haemodiafiltration, solutions for (0861)**

**Definition:** addition of all types of antioxidants is prohibited,

thus the example of metabisulfite salts has been deleted.

**Hydroxyfurfural:** the test is carried out only if glucose is added to the preparation.

**Aluminium:** the way the pH is adjusted is stated.

**Sodium:** atomic absorption spectrometry method replaced by an atomic emission spectrometry method. Sodium emits as a doublet at 589.0 nm and 589.6 nm. Both wavelengths are therefore mentioned.

**Lactate and hydrogen carbonate:** the supplier of the column recommends a maximum temperature of 65 °C. At 85 °C rapid column ageing occurs. Supportive data has shown that the accuracy and the precision at 60 °C were similar to those at 85 °C. The slight shift in retention time does not affect the resolution. Therefore the temperature of the column has been lowered to 60 °C.

### **Heparin calcium (0332)**

### **Heparin sodium (0333)**

These monographs have been thoroughly revised further to the contamination events in 2008 to ensure appropriate quality control for unfractionated heparin. The style and presentation have also been updated in line with the current version of the Style guide.

**Definition:** the minimum potency limit has been raised after an enquiry among European manufacturers regarding the quality of currently marketed heparin batches; only 1 grade of heparin has been kept as the present 2-tiered specification no longer reflects the situation in Europe.

**Production:** the nuclear magnetic resonance (NMR) spectrometry and capillary electrophoresis tests previously introduced in the 1<sup>st</sup>-step revision applicable from 1 August 2008 have been deleted, as detailed tests are now provided under Identification and Tests; statements have been added to emphasise the need for a reliable quality management system throughout production and, based on current practice among European manufacturers, for confirming the identity of the source species as well as the absence of any material issued from other species likely to contaminate the drug substance. The monographs have also been revised to harmonise the information related to the source species for substances of human and animal origin and its presentation in monographs. The statement relative to the origin of the substance has been moved under Definition accordingly and a paragraph has been added regarding the health of the animals used for the preparation of heparin.

**Identification:** the specific optical rotation and zone electrophoresis tests have been replaced by highly specific <sup>1</sup>H-NMR and strong anion-exchange liquid chromatography (SAX-HPLC) tests; <sup>1</sup>H-NMR has been selected for its ability not only to allow identification of heparin, but also to alert users to possible contamination; identification of the counterion for heparin sodium is now based on the test for sodium by atomic absorption spectrometry described under Tests.

**Nucleotidic impurities:** the limit has been tightened, based on current batch data.

**Protein:** the Lowry test method has been introduced to replace the absorbance test.

**Related substances:** a SAX-HPLC-based test has been introduced, allowing the differentiation of natural contaminants linked to the production process (such as dermatan sulfate and chondroitin sulfate) from chemically synthesised contaminants; a limit has been set for the sum of dermatan sulfate and chondroitin sulfate, which co-elute in this method, further to consideration of current batch data.

**Nitrogen:** a lower limit has been added, based on current batch data.

**Heavy metals:** method C has been replaced by method F, in line with the general policy for heavy metal tests.

**Sulfated ash:** in view of the highly specific tests introduced in the monograph, this test has become redundant and has therefore been deleted.

### **Human antithrombin III concentrate (0878)**

### **Human coagulation factor VII (1224)**

**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 (CHMP) of the European Medicines Agency (EMA) 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 monographs. 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 IX (1223)**

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production; the BET acceptance criteria approved by the US FDA for replacement of the pyrogen test. The endotoxin limit is in line with that in the monograph *Human coagulation factor VIII (0275)* published in Supplement 6.6 of the Ph. Eur.

#### **Human coagulation factor XI (1644)**

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#### **Human fibrinogen (0024)**

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product; feasibility in light of experience with current production; the BET acceptance criteria approved by the US FDA for replacement of the pyrogen test. Since there are different concentrations of human fibrinogen on the market, the endotoxin limit is expressed in International Units per milligram of fibrinogen instead of per millilitre of the preparation to be examined.

#### **Human normal immunoglobulin (0338)**

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

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

**Sodium:** precision of limit modified in accordance with general policy.

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#### **Human prothrombin complex (0554)**

#### **Human von Willebrand factor (2298)**

**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 (CHMP) of the European Medicines Agency (EMA) 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 monographs. 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.

#### Hydrocortisone (0335)

**Related substances:** limit for impurity G increased, based on current batch data.

#### Insulin, human (0838)

**Production:** the monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and its presentation. A paragraph has been added accordingly regarding the health of the animals used for the preparation of human insulin.

#### Ioxaglic acid (2009)

**Related substances:** identification of peaks moved from system suitability requirements to identification of impurities paragraph, and retention time and relative retentions moved from system suitability requirements to a separate paragraph, in line with current policy.

#### Isoprenaline hydrochloride (1332)

**Identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** system suitability criterion modified to be in line with current policy; relative retentions of impurity A and orciprenaline introduced; explicit acceptance criterion for unspecified impurities introduced; disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose  $\leq 2$  g/day).

#### Isotretinoin (1019)

**Identification:** UV identification deleted.

**Related substances:** method and limits updated.

**Assay:** modified to reduce use of toxic solvents/reagents.

**Storage:** indication of temperature deleted, 'under inert gas' added.

**Impurities:** section updated.

#### Itraconazole (1335)

**Related substances:** the possibility of using a column with a particle size of 3.5  $\mu\text{m}$  has been added.

#### Levodropropizine (1535)

**Impurity C:** limit for this impurity decreased to 5 ppm; signal-to-noise ratio requirement introduced.

#### Lisinopril dihydrate (1120)

**IR identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** new reference standard introduced to ensure peak assignment of impurity F; system suitability criteria modified; resolution between impurities B and A introduced and peak-to-valley ratio between impurity E and lisinopril decreased from 9 to 7; explicit acceptance criterion for unspecified impurities introduced.

#### Meclozine dihydrochloride (0622)

**Characters:** appearance modified as substance is described as slightly hygroscopic.

**Identification:** description of sample preparation deleted in identification test B in accordance with current policy; TLC in identification test C modified to avoid use of methylene chloride.

**Appearance of solution:** test deleted since substance not used parenterally.

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

**Impurities:** transparency list introduced.

#### Methylphenobarbital (0189)

**Content:** lower limit decreased based on repeatability results following change in assay solvent.

**Identification C:** chloroform replaced by less-toxic methylene chloride.

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

**Assay:** modified to avoid use of pyridine.

**Impurities:** section added describing impurity controlled by LC.

#### Nicotinic acid (0459)

**Identification:** identification C modified to avoid use of toxic reagents.

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

**Impurities:** section introduced showing impurities controlled by LC.

#### Nimesulide (1548)

**Identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** impurities A to F defined as specified impurities, with corresponding reference standard for their identification; wording aligned with general policy; disregard limit increased to 0.05 per cent in line with general monograph *Substances for pharmaceutical use (2034)*.

**Impurities:** impurities A to F now listed as specified impurities and impurity G listed as other detectable impurity.

#### Ofloxacin (1455)

**Related substances:** paragraph for identification of impurities introduced; explicit acceptance criterion for unspecified impurities introduced; disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose  $\leq 2$  g/day).

#### Omeprazole sodium (1032)

**Identification:** TLC and UV replaced by IR; optical rotation test added to differentiate racemic form from esomeprazole sodium.

**Impurity C:** TLC test deleted since impurity now covered by related substances test.

**Related substances:** CRS for peak identification integrated; run time of LC prolonged to allow detection of impurity C; limits updated.

**Impurities:** impurities D and E now listed as specified impurities and impurity C listed as other detectable impurity.

#### Pancreas powder (0350)

**Production:** monograph revised to harmonise the information related to the source species for substances of human and animal origin and its presentation; the section has been added accordingly with a paragraph regarding the health of the animals used for the preparation of pancreas powder.

#### Peritoneal dialysis, solutions for (0862)

**Definition:** addition of all types of antioxidants is prohibited, thus the example of metabisulfite salts has been deleted.

**Hydroxyfurfural:** the test is carried out only if glucose is added to the preparation.

**Aluminium:** the way the pH is adjusted is stated.

**Sodium:** atomic absorption spectrometry method replaced by an atomic emission spectrometry method. Sodium emits as a doublet at 589.0 nm and 589.6 nm. Both wavelengths are therefore mentioned.

**Lactate and hydrogen carbonate:** the supplier of the column recommends a maximum temperature of 65 °C. At 85 °C rapid column ageing occurs. Supportive data have shown that the accuracy and the precision at 60 °C were similar to that at 85 °C. The slight shift in retention time does not affect the resolution. Therefore the temperature of the column has been lowered to 60 °C.

#### Phentolamine mesilate (1138)

**Content:** upper limit for titrimetric assays aligned with Technical Guide requirements.

**Identification C:** IR reference spectrum replaced by CRS in accordance with current policy.

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

**Impurities:** addition of other detectable impurities B and C.

#### Phloroglucinol, anhydrous (2301)

#### Phloroglucinol dihydrate (2302)

**Related substances:** new LC method introduced, reflecting impurity profiles of current batches.

**Sulfates:** water replaced by distilled water.

**Heavy metals:** mineralisation-free alternative to method F introduced (method H).

**Impurities:** section added describing impurities controlled by LC.

#### Polysorbate 80 (0428)

**Peroxide value:** preparation of the solution to be titrated has been modified.

**Ethylene oxide and dioxan:** the definitions of  $C_{E0}$  and  $C_D$  have been corrected.

#### Protamine hydrochloride (0686)

**Production:** this monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and its presentation; a paragraph has been added accordingly regarding the health of the animals used for the preparation of protamine hydrochloride; the statement on minimising the risk of microbial contamination has been deleted in line with the general policy for cross-references as this aspect is already covered by general chapter 5.1.7.

**Barium:** precision of limit modified in accordance with general policy.

#### Protamine sulfate (0569)

**Production:** this monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and its presentation; a paragraph has been added accordingly regarding the health of the animals used for the preparation of protamine sulfate; the statement on minimising the risk of microbial contamination has been deleted in line with the general policy for cross-references as this aspect is already covered by general chapter 5.1.7.

#### Risperidone (1559)

**Related substances:** additional impurities have been introduced to the transparency list, derived from an alternative synthetic pathway; a paragraph for impurity identification has been added.

#### Salbutamol (0529)

**Related substances:** a paragraph for the identification of

impurities B, D, F and G has been introduced; an explicit acceptance criterion for unspecified impurities has been introduced; the disregard limit is now described with reference to the area of the principal peak in a new reference solution (c), according to current policy.

#### Sertraline hydrochloride (1705)

**Identification:** cross reference to LC test for enantiomeric purity added as alternative to test for specific optical rotation.

**Impurity E:** TLC replaced by LC in accordance with current policy.

#### Silica, colloidal anhydrous (0434)

**Functionality-related characteristics:** the section was added, with the following FRC for colloidal anhydrous silica used as glidant in tablets and capsules: specific surface area.

#### Silica, dental type (1562)

**Functionality-related characteristics:** the section was added, with the following FRC for dental type silica used as abrasive: specific surface area.

#### Silica, hydrophobic colloidal (2208)

**Functionality-related characteristics:** the section was added, with the following FRC for hydrophobic colloidal silica used as glidant in tablets and capsules: specific surface area.

#### Sodium ascorbate (1791)

**Related substances:** impurities C and D, determined by external standards, are excluded from the calculation of the total.

**Copper, Iron, Nickel:** precision of limits modified in accordance with general policy.

#### Sodium hyaluronate (1472)

**Definition and Production:** this monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and the presentation of this information. The statement relative to the origin of the substance has been moved under Definition accordingly and a paragraph has been added regarding the health of the animals used for the preparation of sodium hyaluronate.

**Iron:** precision of limit modified in accordance with general policy.

#### Sodium lactate solution (1151)

**Definition:** revised to indicate unambiguously that the 1<sup>st</sup> part of the statements of the content relates to the declared content and that the 2<sup>nd</sup> part relates to the measured assay.

**Aluminium:** concentration of the test solution has been increased so that the calibration curve covers the entire range of the expected test results.

#### Sodium propyl parahydroxybenzoate (1263)

**Definition:** limits of content modified as assay is performed by LC.

**Characters:** added that substance is hygroscopic.

**Identification:** tests B and E sufficient as first identification; test D deleted.

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

**Assay:** titration replaced by LC used in test for related substances.

**Storage:** use of airtight container added since substance is hygroscopic.

**Impurities:** impurity A now listed as specified impurity.

#### Somatostatin (0949)

**Definition:** further to the establishment of the latest batches of *somatostatin CRS*, and due to a risk of overestimation

of content of batches, the upper content limit is raised to 104 per cent.

#### **Spironolactone (0688)**

**Identification:** IR now performed on solid state to avoid use of chloroform; corresponding recrystallisation procedure added since substance shows polymorphism.

**Specific optical rotation:** ethanol (96 per cent) used as solvent instead of chloroform; limits modified accordingly.

**Related substances:** new LC method developed (selective to all potential related substances); corresponding Impurities section introduced.

**Assay:** absorbance test replaced by LC; limits for content updated accordingly.

#### **Sulfinpyrazone (0790)**

**Identification C:** description of sample preparation deleted in accordance with current policy.

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

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

**Impurities:** specified impurity C added.

#### **Talc (0438)**

**Calcium and Lead:** precision of limits modified in accordance with general policy.

**Functionality-related characteristics:** the section was added, with the following FRCs for talc used as lubricant or glidant in tablets and capsules and as antiadhesive in coated and film-coated tablets: particle-size distribution by laser diffraction (particle size would not allow analytical sieving); specific surface area.

#### **Timolol maleate (0572)**

**Identification C:** TLC previously described in related substances test adapted for identification purposes only.

**Enantiomeric purity:** limit indicated according to current policy.

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

**Impurities:** list of impurities modified according to revision of test for related substances.

#### **Titanium dioxide (0150)**

**Functionality-related characteristics:** the section was added, with the following FRCs for titanium dioxide used as opacifier in solid oral dosage forms and in preparations for cutaneous application: particle-size distribution by laser diffraction (the particles are too small to allow sieving); bulk and tapped density. The tests were added because titanium dioxide is marketed as a fine powder consisting of particles a few micrometres in size as well as an agglomerated powder, and it can crystallise in 2 forms, anatase and rutile, that have different physical properties, e.g. density.

#### **$\alpha$ -Tocopheryl acetate concentrate (powder form) (0691)**

**Identification:** GC used for assay added as first identification; TLC using ether kept as second identification only.

**Related substances:** test deleted since it has to be carried

out at active-substance level (monograph *all-rac- $\alpha$ -Tocopheryl acetate (0439)*).

**Assay:** obsolete packed GC column replaced with capillary column; use of chromatographic conditions described in monograph *all-rac- $\alpha$ -Tocopheryl acetate (0439)*.

#### **Tolbutamide (0304)**

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

**Heavy metals:** limit decreased based on daily intake and treatment duration.

**Storage:** storage in airtight container indicated.

**Impurities:** section added describing impurities controlled by LC.

#### **Tretinoin (0693)**

**Identification:** UV identification deleted.

**Related substances:** method and limits updated.

**Loss on drying:** conditions harmonised with those of *Isotretinoin (1019)*.

**Assay:** modified to reduce use of toxic solvents/reagents.

**Storage:** indication of temperature deleted, 'under inert gas' added.

**Impurities:** section updated.

#### **Triflusal (1377)**

**Identification:** description of sample preparation deleted in accordance with current policy.

**Related substances:** paragraph for identification of impurities and explicit acceptance criterion for unspecified impurities introduced; relative retentions of unspecified impurities A, C and D deleted; disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose  $\leq 2$  g/day).

#### **Tropicamide (1159)**

**Identification C:** description of sample preparation deleted in accordance with current policy.

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

**Tropic acid:** test deleted since impurity C now detected by LC in test for related substances.

**Impurities:** addition of specified impurity D.

#### **Trypsin (0694)**

**Definition:** this monograph has been revised to harmonise the information related to the source species for substances of human and animal origin and its presentation; an editorial modification has therefore been made to the statement concerning the origin of the substance under Definition, to align it with that of similar monographs.

**Labelling:** the section has been harmonised with the monograph *Chymotrypsin (0476)*.

#### **Zolpidem tartrate (1280)**

**Related substances:** relative retention of impurity A introduced; explicit acceptance criterion for unspecified impurities introduced; disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose  $\leq 2$  g/day).

**Impurities:** impurity A now listed as other detectable impurity.