

## COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 5.8

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the June 2006 session. This information completes the modifications indicated by lines in the margin in the supplement. Therefore, the information below is not necessarily exhaustive.

### ANALYTICAL METHODS

#### 2.6.7. Mycoplasmas

Culture method: a reference to the new low-passage strain BRPs has been introduced.

Nutritive properties: the validity criterion has been defined more precisely.

Test for mycoplasmas in the product to be examined: one of the invalidity criteria has been clarified.

Nucleid acid amplification techniques: a new section has been introduced followed by recommendations on the validation of such tests, either as an alternative to the culture and/or indicator cell culture method or as an official test where so prescribed in a monograph.

### GENERAL MONOGRAPHS

#### Allergen products (1063)

Production: addition of a reference to new chapter 5.1.7. *Viral safety*.

#### Extracts (0765)

Definition: addition of a reference to new chapter 5.1.7. *Viral safety*.

#### Immunosera for human use, animal (0084)

Production: under General provisions, addition of a reference to new chapter 5.1.7. *Viral safety*.

#### Monoclonal antibodies for human use (2031)

Production: under General provisions, addition of a reference to new chapter 5.1.7. *Viral safety*.

#### Recombinant DNA technology, products of (0784)

Production: addition of a reference to new chapter 5.1.7. *Viral safety*.

#### Substances for pharmaceutical use (2034)

Definition: addition of a reference to new chapter 5.1.7. *Viral safety*.

#### Vaccines for human use (0153)

Production: under General provisions, addition of a reference to new chapter 5.1.7. *Viral safety*.

#### Vegetable fatty oils (1579)

The occurrence of polyaromatic hydrocarbons in vegetable oils is largely related to the drying of the seeds, where combustion gases may come into contact with the seeds. As of 1<sup>st</sup> May 2005, benzo[a]pyrene has to be controlled in oils according to food regulations in force in the EU. The revision of the monograph reflects this new legal framework.

### DOSAGE FORMS

#### Tablets (0478)

A new sub-section on oral lyophilisates is introduced, comprising a definition, a production section and tests

for disintegration and water content. Oral lyophilisates have to comply with the test for uniformity of dosage units or, where justified and authorised, with the test for uniformity of content.

### VACCINES FOR VETERINARY USE

#### Rabies vaccine for human use prepared in cell cultures (0216)

Residual host-cell DNA: the upper limit has been increased from 100 pg to 10 ng per single human dose for the following reasons: no scientific data have shown that 100 pg per single human dose is more safe than 10 ng per single human dose; harmonisation with chapter 5.2.3. *Cell substrates for*

*the production of vaccines for human use*; harmonisation with the recently revised WHO recommendations, particularly since rabies vaccines for human use prepared in cell cultures are produced mainly for non-European countries; all rabies vaccines for human use prepared in cell cultures comply with the 10 ng per single human dose requirement, which is not the case with the limit of 100 pg per single human dose.

## HOMOEOPATHIC PREPARATIONS

Definition: under raw materials, addition of a reference to new chapter 5.1.7. *Viral safety*.

### MONOGRAPHS

#### **Adrenaline tartrate (0254)**

Identification A: revision of the procedure to avoid the use of ether; slight change to the lower limit, for harmonisation with the future monograph on adrenaline and with the USP.

Identification B: description of a more detailed procedure for the CRS.

Related substances: replacement of the absorbance test for adrenalone and of the TLC for noradrenaline by an LC, in accordance with current policy.

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

#### **Ampicillin trihydrate (0168)**

Definition: upper limit for content increased to 102.0 per cent as the assay is performed by LC.

Assay: deletion of some system suitability criteria that are no longer required in the monograph following the application of general chapter 2.2.46. *Chromatographic separation techniques*.

Storage: deletion of the maximal temperature indicated.

Impurities: addition of new impurity N.

#### **Bisacodyl (0595)**

Related substances: the CRS is now accompanied by a chromatogram to be used for peak identification and the preparation of reference solution (b) has been modified.

#### **Bromocriptine mesilate (0596)**

Related substances: since the peaks due to impurities A and B can be easily distinguished by their respective heights, an individual impurity A CRS is no longer needed and reference solution (d) has therefore been deleted.

#### **Calcium lactate, anhydrous (2118)**

#### **Calcium lactate monohydrate (2117)**

#### **Calcium lactate pentahydrate (0468)**

#### **Calcium lactate trihydrate (0469)**

Related substances: as a matter of general policy it has been decided not to include a test for related substances (covering the inactive moiety) in monographs on inorganic substances, and consequently, this test has been deleted from the 4 monographs on calcium lactate salts.

#### **Calcium phosphate (1052)**

Fluorides: Method I is replaced by Method II in the potentiometric determination.

#### **Capsicum (1859)**

Nonivamide: recent experiments have indicated that the resolution between nonivamide and capsaicin is less than 3.0, and a limit of 0.5 has been indicated; reference standards for capsaicin and nonivamide have been introduced.

Assay: a reference standard for capsaicin has been introduced.

#### **Capsicum oleoresin, refined and quantified (2336)**

Nonivamide: recent work has indicated that the resolution between nonivamide and capsaicin is less than 3.0, and a limit of 1.5 has been indicated.

#### **Capsicum tincture, standardised (2337)**

Nonivamide: recent work has indicated that the resolution between nonivamide and capsaicin is less than 3.0, and a limit of 1.5 has been indicated.

#### **Castor oil, hydrogenated (1497)**

Characters: the solubilities have been reviewed.

#### **Cilastatin sodium (1408)**

Characters: the solubility in dimethyl sulphoxide has been modified based on experimental results.

#### **Desmopressin (0712)**

Amino acids analysis: this test has been moved from the Tests section to the Identification section to reflect the general policy to be followed for synthetic peptides; in addition, a 10 per cent tolerance has been applied to the limits for the relative proportions of the amino acids, better reflecting the accuracy of the method.

Labelling: the information relating to bacterial endotoxins has been deleted since it is already covered by the general monograph *Substances for pharmaceutical use (2034)*.

#### **Dihydrostreptomycin sulphate for veterinary use (0485)**

Identification: 2 series are now described; the 1<sup>st</sup> identification includes the new LC assay and identification of sulphates so the test for sulphates has been deleted under Tests.

Streptomycin: this compound also contributes to the activity and is now considered in the assay, so the corresponding test has been deleted.

Related substances: a test by LC has been added.

Assay: an LC method replaces the microbiological assay, in accordance with current policy for antibiotics.

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

Methanol: this class 2 solvent test has been deleted according to current policy.

**Dopexamine dihydrochloride (1748)**

Heavy metals: method C has been replaced by method A to avoid the risk of loss of metals during the digestion of the sample.

Water: due to difficulties in carrying out the test on 2.000 g, the sample weight has been reduced.

Assay: it is necessary to perform the titration immediately after preparation of the test solution due to possible acetylation of the substance.

**Enalaprilat dihydrate (1749)**

Related substances: due to a problem of availability of a satisfactory spiked sample, enalaprilat for peak identification CRS (containing impurity G) is replaced by enalaprilat impurity G CRS.

**Enoxaparin sodium (1097)**

Definition: a specification for anti-factor IIa activity has been included to provide better control; the previous version of the monograph had a specification only for the anti-factor Xa/anti-factor IIa ratio.

**Fluphenazine dihydrochloride (0904)**

Title: title corrected.

Definition: symmetrical limits prescribed.

Identification: harmonisation of identification test C with the one described in the monographs on fluphenazine decanoate and fluphenazine enantate, and suppression of identification test D.

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

Sulphated ash: use of a platinum crucible, as the substance contains fluoride.

Assay: introduction of the usual warning.

Impurities: list completed.

**Hypromellose phthalate (0347)**

Free phthalic acid: cyanoacetic acid has been replaced by trifluoroacetic acid (baseline is more stable) in the mobile phase, within the framework of international harmonisation.

Chlorides: the changes have been approved within the framework of international harmonisation.

Water: the change has been approved within the framework of the international harmonisation.

Apparent viscosity: this functionality-related characteristic has been indicated for hypromellose phthalate used as gastro-resistant coating agent.

Solubility: this functionality-related characteristic has been indicated for hypromellose phthalate used as gastro-resistant coating agent.

**myo-Inositol (1805)**

Conductivity: the limit has been slightly increased to take into account the change in the measurement temperature in the revised method (2.2.38) and the batch results.

Lead: due to a problem of solubility, the preparation of the test solution has been revised.

**Oxytocin (0780)**

Amino acid analysis: this test has been moved from the Tests section to the Identification section to reflect the general policy to be followed for synthetic peptides; in addition, a 10 per cent tolerance has been applied to the limits for the relative proportions of the amino acids, better reflecting the accuracy of the method.

Labelling: the information relating to bacterial endotoxins has been deleted since it is already covered by the general monograph *Substances for pharmaceutical use (2034)*.

**Oxytocin concentrated solution (0779)**

Title: it has been amended according to the general policy regarding terminology.

Amino acid analysis: this test has been moved from the Tests section to the Identification section to reflect the general policy to be followed for synthetic peptides; in addition, a 10 per cent tolerance has been applied to the limits for the relative proportions of the amino acids, better reflecting the accuracy of the method.

Labelling: the information relating to bacterial endotoxins has been deleted since it is already covered by the general monograph *Substances for pharmaceutical use (2034)*.

**Poloxamers (1464)**

Characters: the solubilities have been reviewed.

**Pravastatin sodium (2059)**

Related substances: impurity E has been added to the list, qualified at 0.2 per cent; the relative retention paragraph has been complemented and the limit for the unspecified impurities has been stipulated.

**Sesame oil, refined (0433)**

Composition of triglycerides: the LC method previously used a refractometer as detector. Instead, it now uses a light-scattering detector, which gives a very stable baseline and allows the separation of peaks that could not be separated when using the RI detector (for example SLL). The monograph now describes a gradient LC system and light scattering detector that allow the detection of other triglycerides, which could not be detected with the isocratic system and the RI detector (such as SOO, PSO, SSL, PPS, SSO) and represent about 12 per cent of the total triglycerides. Since the response of the ELS detector was not always completely linear, a calibration using triolein (OOO) has also been introduced for the quantification. A collaborative study among 5 laboratories has been successfully carried out. Based on the results, it appeared necessary to change the limits for the triglycerides OOL and POL.

**Sodium aurothiomalate (1994)**

Identification A: the monograph was adapted from the BP, and a phase in the original BP monograph that was omitted from the text has been reintroduced.

Identification B: the procedure has been specified, as additions of H<sub>2</sub>O<sub>2</sub> and an alkaline agent are not justified, and nor are the filtration and extraction procedures.

Related substances: methanol R2 is used in the mobile phase as detection is at 205 nm.

### Somatostatin (0949)

Amino acids analysis: this test has been moved from the Tests section to the Identification section to reflect the general policy to be followed for synthetic peptides; in addition, a 10 per cent tolerance has been applied to the limits for the relative proportions of the amino acids, better reflecting the accuracy of the method.

Labelling: this section has been deleted since the information it contained is already covered by the general monograph *Substances for pharmaceutical use (2034)*.

### Somatropin (0951)

Related proteins: a new somatropin/desamidomatropin resolution mixture CRS has been introduced, the use of which will avoid early depletion of somatropin CRS stocks; moreover, unlike somatropin CRS, somatropin/desamidomatropin resolution mixture CRS will not require storage at room temperature for 24 h prior to use.

Charged variants: several adjustments have been made to this test (capillary electrophoresis), taking account, notably, of the establishment of the somatropin CRS batch 2: further flexibility has been introduced in the method description, for instance with regard to the length of the capillary, the sample injection and rinsing times; the detection wavelength has been increased in order to allow the use of classical UV detectors; the isoform I<sub>5</sub> peak has been deleted since it may not be detected in the somatropin CRS batch 2 and has sometimes been confused with the 2<sup>nd</sup> peak of the isoform I<sub>4</sub> doublet; the note identifying the isoform I<sub>3</sub> peak as Gln-18 somatropin has been deleted since it has been reported that, depending on the sample considered, it may correspond to other somatropin variants; the relative migration time is now only indicated for isoform I<sub>4</sub> as it is the only impurity characterised by an individual limit; the given specifications for the relative migration time of isoform I<sub>4</sub> correspond to a range based on the outcome of the establishment study.

Labelling: the information relating to bacterial endotoxins has been deleted as it is already covered by the general monograph *Substances for pharmaceutical use (2034)*.

### Somatropin concentrated solution (0950)

Title: it has been amended according to the general policy regarding terminology.

Related proteins: a new somatropin/desamidomatropin resolution mixture CRS has been introduced, the use of which will avoid early depletion of somatropin CRS stocks; moreover, unlike somatropin CRS, somatropin/desamidomatropin resolution mixture CRS will not require storage at room temperature for 24 h prior to use.

Charged variants: several adjustments have been made to this test (capillary electrophoresis), taking account, notably, of the establishment of the somatropin CRS batch 2: further flexibility has been introduced in the method description, for instance with regard to the length of the capillary, the sample injection and rinsing times; the detection wavelength has been increased

in order to allow the use of classical UV detectors; the isoform I<sub>5</sub> peak has been deleted since it may not be detected in the somatropin CRS batch 2 and has sometimes been confused with the 2<sup>nd</sup> peak of the isoform I<sub>4</sub> doublet; the note identifying the isoform I<sub>3</sub> peak as Gln-18 somatropin has been deleted since it has been reported that, depending on the sample considered, it may correspond to other somatropin variants; the relative migration time is now only indicated for isoform I<sub>4</sub> as it is the only impurity characterised by an individual limit; the given specifications for the relative migration time of the isoform I<sub>4</sub> correspond to a range based on the outcome of the establishment study.

Labelling: the information relating to bacterial endotoxins has been deleted as it is already covered by the general monograph *Substances for pharmaceutical use (2034)*.

### Somatropin for injection (0952)

Related proteins: a new somatropin/desamidomatropin resolution mixture CRS has been introduced, the use of which will avoid early depletion of somatropin CRS stocks; moreover, unlike somatropin CRS, somatropin/desamidomatropin resolution mixture CRS will not require storage at room temperature for 24 h prior to use.

Charged variants: several adjustments have been made to this test (capillary electrophoresis), taking account, notably, of the establishment of the somatropin CRS batch 2: further flexibility has been introduced in the method description, for instance with regard to the length of the capillary, the sample injection and rinsing times; the detection wavelength has been increased in order to allow the use of classical UV detectors; the isoform I<sub>5</sub> peak has been deleted since it may not be detected in the somatropin CRS batch 2 and has sometimes been confused with the 2<sup>nd</sup> peak of the isoform I<sub>4</sub> doublet; the note identifying the isoform I<sub>3</sub> peak as Gln-18 somatropin has been deleted since it has been reported that, depending on the sample considered, it may correspond to other somatropin variants; the relative migration time is now only indicated for isoform I<sub>4</sub> as it is the only impurity characterised by an individual limit; the given specifications for the relative migration time of isoform I<sub>4</sub> correspond to a range based on the outcome of the establishment study.

### Sulbactam sodium (2209)

pH: limits widened in light of current batch data for the non-sterile product; previous limits, as in the Japanese Pharmacopoeia, applied in fact to the sterile product.

### Terazosin hydrochloride dihydrate (2021)

Related substances: impurity E cannot be included in terazosin for system suitability CRS and a CRS of the individual impurity is now injected; the relative retention of some impurities may vary and the paragraph giving the relative retentions has been replaced by a paragraph on the identification of the impurities, making reference to the CRS injected; an additional adjustment is now described in case of insufficient separation of the impurities.

**Thioridazine (2005)**

This revision proposal is based on the recently adopted revised monograph Thioridazine hydrochloride (0586).

**Tranexamic acid (0875)**

Related substances: it has not been possible to obtain a sample of impurity C for establishment of a CRS replacement batch, so, as impurity C is present in tranexamic acid CRS, this CRS is now injected for peak

identification of impurity C; the criterion for system suitability has been adapted; as impurity D is available as a reagent, it is now injected for peak identification.

**Triglycerol diisostearate (2032)**

Since this product contains more than 100 components (linear or branched chains), it is not possible to identify all the peaks, even using GC-MS. A limit for the sum of the peaks eluting between C16 and C18 is proposed, together with a limit for the sum C14 + C16 + C18.

## LIST OF CODES OF GROUPS OF EXPERTS

(July 2006)

### GROUPS OF EXPERTS

1	Microbiology	11	Organic chemistry - natural products
6	Biological substances	12	Galenical products
6B	Human blood and blood products	13A	Phytochemistry
7	Antibiotics	13B	Phytochemistry
9G	Medicinal gases	13H	Fatty oils and derivatives
10A	Organic chemistry - synthetic products	14	Radioactive compounds
10B	Organic chemistry - synthetic products	15	Sera and vaccines
10C	Organic chemistry - synthetic Products	15V	Veterinary sera and vaccines
10D	Organic chemistry - synthetic Products		

### WORKING PARTIES

BOT	Botulinum toxin	LEC	Lecithins for pharmaceutical purposes
BSR	Bovine serum	MAB	Monoclonal antibodies
CEL	Cellulose derivatives	MAT	Monocyte activation test
CLP	Cloud point	MMM	Alternative microbiological methods
CND	Conductivity	MYC	Mycoplasmas
CRB	Carbohydrates	NIR	Near-infrared spectrophotometry
CST	Chromatographic separation techniques	NMR	Nuclear magnetic resonance spectrometry
CTP	Cell therapy products	P4	Procedure 4
FRC	Functionality-related characteristics	POW	Powder characterisation techniques
GEL	Gelatin	PST	Pesticides in herbal drugs
GTP	Gene therapy products	RGN	Reagents
HFA	Propellants	SRP	Special revision programme
HMM	Homoeopathic manufacturing methods	ST	Standard terms
HOM	Homeopathy	STA	Statistics
ICP	Inductively coupled plasma spectrometry	VIT	Vitamins
INC	Inorganic chemistry	WAT	Water
INH	Inhalations	WXT	Water for the preparation of extracts