

## Comments Concerning Revised Texts Published in Supplement 6.8

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

### GENERAL TEXTS

#### 1. General notices

**Limits:** the text has been modified to clarify the interpretation of limits in relation to the rounding rules applied to the values stated in Pharmacopoeial monographs. The new statement clarifies that trailing zeros are considered significant when stated in compendia limits, which is in line with USP and JP practices.

#### 2.4.8. Heavy metals

Method H has been developed, due to potential losses of analyte during the ignition procedure when using methods C and D. It involves:

- dissolution of the test substance in mixtures of water and organic solvent or in organic solvents,
  - reduced amount of test substance,
  - comparison of the spots obtained with 0.45 µm filters.
- Editorial changes have been made to the description of system suitability and acceptance criteria.

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

To ease dissolution of the internal standard in test solution (a) and reference solutions (a1) and (a2), gentle heating of the preparation is allowed.

#### 2.4.32. Total cholesterol in oils rich in omega-3 acids

**Reference solution (b):** the internal standard stock solution has been added; to improve the concentration agreement between reference solution (b) and the test solution (which has a lower concentration in production batches), reference solution (b) has been diluted 10-fold.

#### 2.6.1. Sterility

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

The following announcement has recently been published on the ATCC website:

“Strain ATCC® 16404TM, currently known as *Aspergillus niger*, has been designated as a quality-control reference strain in a number of applications. It is also cited as the standard culture in several official methods (USP) and manuals, as well as the Code of Federal Regulations. Recently, a polyphasic study was performed at ATCC in which molecular data was combined with physiological characteristics. The results clearly indicate that ATCC® 16404TM is a member of the novel species *Aspergillus brasiliensis*. Thus, we are renaming ATCC®16404TM as *Aspergillus brasiliensis* and will be notifying users worldwide of this name change.

A recent publication [Varga et al., International Journal of Systematic and Evolutionary Microbiology (2007) 57: 1925-1932] describes the novel species. ATCC® 9642TM, deposited as *Aspergillus niger*, is also being renamed as *Aspergillus brasiliensis*.”

As a consequence of this reclassification, the name *Aspergillus niger* has been replaced by the name *Aspergillus brasiliensis* in the present chapter. This has

no impact on the characterisation of the micro-organism and on the performance of the test.

#### 2.6.21. Nucleic acid amplification techniques

This chapter has been revised to include a validation guideline for the quantification of B19 virus DNA in plasma pools. This guideline has been initially developed in the framework of the OMCL network for the validation of the method in the context of Official Control Authority Batch Release (OCABR).

This guideline is given for information: it does not form a mandatory part of the Pharmacopoeia.

#### 2.9.3. Dissolution test for solid dosage forms

This chapter has been corrected to delete the section Guidance on dissolution testing that was included at the end of the chapter and was purely Ph. Eur. text. What remains in chapter 2.9.3 corresponds to the internationally harmonised chapter and is legally binding.

The recommendations on dissolution testing are now included in the new non-mandatory chapter 5.17.1. *Recommendations on dissolution testing*.

#### 2.9.34. Bulk density and tapped density of powders

As a result of the pharmacopoeial harmonisation process, the following revisions have been made.

**Bulk density/Method 2:** the tolerance for the cup dimensions has been corrected.

**Tapped density/Method 3:** a sentence has been added, requesting that the test conditions be stated with the results.

**Compressibility index:** a sentence has been added, requesting that V10 be mentioned if it is used.

#### 3.2.1. Glass containers for pharmaceutical use

Test B. Hydrolytic resistance of glass grains: the limits have been corrected to fit with the ISO 720 (1985) standard. The equivalence of alkali expressed as mass of Na<sub>2</sub>O per gram of glass has been deleted because this information is redundant.

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

**Routine testing of designated SPF flocks:** based on data and statistical arguments about mortality of SPF chickens, the 0.1 per cent maximum weekly mortality has been increased to 0.2 per cent for initiating investigations on bird carcasses; a mortality of 0.2 per cent is still considered as “normal” and gives a satisfactory level of quality.

#### 5.17.1. Recommendations on dissolution testing

This chapter gives recommendations on dissolution testing, previously included at the end of chapter 2.9.3. *Dissolution test for solid dosage forms*, the rest of which has undergone pharmacopoeial harmonisation. The

part on recommendations is a purely Ph. Eur. text. The following modifications have also been made. Experimental testing conditions: the presence of enzymes, surfactants, etc. in dissolution media in specific cases is now stated to be subject to approval by the competent authority.

**Recommended dissolution media:** 'artificial gastric juice' is renamed 'simulated gastric juice'; 'hydrochloric acid pH 1.5' is prepared using 1 M hydrochloric acid instead of hydrochloric acid R.

**Expression of dissolution specifications for oral dosage forms:** interpretation of acceptance criteria is clarified.

## GENERAL MONOGRAPHS

### Herbal drugs (1433)

**Definition:** changes introduced to terminology used in general monographs *Herbal drugs (1433)* and *Herbal drug preparations (1434)* to clarify respective scopes.

**Foreign matter:** clarification introduced for requirements on foreign matter for cut herbal drugs in accordance with new definition for cut herbal drugs.

**Heavy metals:** limits introduced for cadmium, lead and mercury.

**Ochratoxin A:** reference made to general method *Determination of ochratoxin A (2.8.22)*.

### Herbal drug preparations (1434)

**Definition:** changes introduced to terminology used in general monographs *Herbal drugs (1433)* and *Herbal drug preparations (1434)* to clarify respective scopes; reference to instant herbal teas removed.

## DOSAGE FORMS

### Premixes for medicated feeding stuffs for veterinary use (1037)

**Active substance:** to ensure a suitable quality of active substances which are not covered by a pharmacopoeial

monograph, compliance with the requirements of the section Down-stream processing of the monograph *Products of fermentation (1468)* has been added as a requirement.

## VACCINES FOR HUMAN USE

### Rabies vaccine (inactivated) for veterinary use (0451)

In order to overcome the high variability in the Potency test and the difficulties encountered in obtaining valid tests and to save a lot of animals without having any impact on the vaccine potency test, the validity criteria have been revised as follows:

- linearity criterion: reduced from 0.05 to 0.01,
- parallelism: reduced from 0.05 to 0.01,
- if the condition for the confidence limits of the estimated potency is the only unsatisfied criterion, the vaccine complies with the test provided that the lower limit is not less than 1 IU in the smallest prescribed dose.

### Vibriosis (cold-water) vaccine (inactivated) for salmonids (1580)

**Immunogenicity:** since small fish cannot be challenged by injection, another suitable route can also be used as long as it is able to induce at least 60 per cent mortality in unvaccinated fish.

**Immunogenicity and Batch potency test:** where justified and when fish cannot be marked, in particular due to their size, and in order to facilitate the practical aspect

of the test, control and vaccinated fish can be kept in the same tank but physically separated (for example by fishing nets). This is the only way to ensure that all the fish are exposed to the same environmental conditions and to avoid the tank effect.

### Vibriosis vaccine (inactivated) for salmonids (1581)

**Definition:** the nomenclature has been updated; *Vibrio anguillarum* has been replaced by *Listonella anguillarum*.

**Immunogenicity:** since small fish cannot be challenged by injection, another suitable route can also be used as long as it is able to induce at least 60 per cent mortality in unvaccinated fish.

**Immunogenicity and Batch potency test:** where justified and when fish cannot be marked, in particular due to their size, and in order to facilitate the practical aspect of the test, control and vaccinated fish can be kept in the same tank but physically separated (for example by fishing nets). This is the only way to ensure that all the fish are exposed to the same environmental conditions and to avoid the tank effect.

## MONOGRAPHS

### Acitrein (1385)

**Characters:** statement on polymorphism added.

**Identification B:** if polymorphs exhibit different spectra, recrystallisation procedure has been used.

### Aniseed (0262)

**Identification B:** illustration of powdered herbal drug added and its description has been adapted accordingly.

### Arachis oil, hydrogenated (1171)

**Water:** hydrogenated oils are obtained from oils which are hydrogenated at 200 °C, bleached at 90 °C under a very low pressure then deodorised at a temperature greater than 190 °C under a pressure of about 5 mm

Hg. As a consequence, the resulting water content is negligible and it is not considered pertinent to guarantee the quality of this oil. Microbial growth is very unlikely to occur on such a substrate.

### Asparagine monohydrate (2086)

**Loss on drying:** conditions have been revised to prevent incomplete drying.

### Atropine (2056)

**Related substances:** impurity B is identified using *atropine impurity B CRS*, as it is not stable in *atropine for peak identification CRS*.

**Azathioprine (0369)**

**Identification:** tests A and C deleted since IR sufficient for identification.

**Acidity or alkalinity:** test deleted since no longer relevant.

**Related substances:** the TLC test has been replaced by an LC test that allows improved control of impurities including chloromethylnitroimidazole and mercaptopurine.

**Betahistine mesilate (1071)**

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

**Related substances:** explicit acceptance criterion for unspecified impurities introduced; disregard limit increased to 0.05 per cent in accordance with current policy.

**Bezafibrate (1394)**

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

**Related substances:** relative retentions of specified impurities A to E and an explicit acceptance criterion for unspecified impurities have been introduced.

**Calcium stearate (0882)**

**Functionality-related characteristics (FRCs):**

this section has been added; the following FRCs are considered useful for calcium stearate used as a lubricant:

- particle-size distribution by laser light diffraction (the particle size would not allow analytical sieving);
- specific surface area: the same conditions as for magnesium stearate are included.

These tests will take into account changes in particle characteristics that might be introduced during the manufacturing process or resulting from the origin of stearic acid.

**Cefradine (0814)**

**Related substances:** instability of *cefradine for peak identification CRS* required the development of a new CRS strategy: 2 reference solutions, containing 2 separate sets of impurities are now described instead of 1 containing all impurities.

**Cetirizine dihydrochloride (1084)**

**Related substances:** limits for the specified impurities have been set at 0.15 per cent; relative retentions of specified impurities and the use of *cetirizine impurity mixture CRS* have been introduced for peak identification; the disregard limit was increased to 0.05 per cent.

**Ciclopirox (1407)**

**Related substances:** the signal-to-noise ratio for impurity B has been deleted because this is already required by chapter 2.2.46; an explicit acceptance criterion for unspecified impurities has been introduced.

**Ciclopirox olamine (1302)**

**Related substances:**

- the signal-to-noise ratio for impurity B has been deleted because this is already required by chapter 2.2.46;
- limit for any impurity has been replaced by limits for impurities B and C; an explicit acceptance criterion for unspecified impurities has been introduced;
- the disregard limit has been decreased to 0.05 per cent in accordance with the current policy.

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

**Clazuril for veterinary use (1714)**

**Identification:** Ph.Eur. reference spectrum for comparison in IR test replaced by a CRS.

**Related substances:** an explicit acceptance criterion for unspecified impurities has been introduced; a system suitability CRS and relative retentions of the specified impurities have been added.

**Impurities:** impurities A to I are now listed as specified impurities.

**Crotamiton (1194)**

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

**Cyproterone acetate (1094)**

**Related substances:**

- impurity mixture CRS has been introduced for peak identification;
- limits and the impurity section have been updated reflecting the quality of current batches.

**Dextromethorphan hydrobromide (0020)**

**Identification:** description of sample preparation for IR deleted in line with current policy.

**Related substances:** values of relative retentions rounded; explicit acceptance criterion introduced for unspecified impurities; limit for any impurity replaced by limit for impurities A, B, C, D.

**Impurities:** impurities A to D now listed as specified impurities.

**Diltiazem hydrochloride (1004)**

**Identification:** quantity of substance to be examined and reference substance to be used for TLC reduced.

**Related substances:** *diltiazem impurity A CRS* replaced by *diltiazem for system suitability CRS* and preparation of reference solutions consequently modified; relative retention for impurity A added; system suitability resolution criterion decreased and symmetry factor requirement for peak due to diltiazem deleted; explicit acceptance criterion introduced for unspecified impurities.

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

**Dobutamine hydrochloride (1200)**

**Identification C:** the method of sample preparation is not specified according to current policy.

**Related substances:** a new reference solution (c) containing a CRS for peak identification of the specified impurities A, B and C has been added in accordance with current policy. The relative retentions of the specified impurities have been added. A correction factor of 1.4 for impurity B has been added. An explicit acceptance criterion for unspecified impurities has been introduced.

**Econazole (2049)**

**Identification:** Ph. Eur. reference spectrum used for comparison in IR test replaced by a CRS.

**Related substances:** explicit acceptance criterion for unspecified impurities has been introduced.

**Econazole nitrate (0665)**

**Definition:** CAS number has been modified.

**Identification:** Ph. Eur. reference spectrum used for

comparison in IR test replaced by a CRS.

**Related substances:** an explicit acceptance criterion for unspecified impurities has been introduced.

#### Enalapril maleate (1420)

**Related substances:** the flow rate has been decreased from 1.4 to 1.0 ml/min; relative retentions of specified impurities and the use of *enalapril impurity mixture CRS* have been introduced for peak identification; an explicit acceptance criterion for unspecified impurities has been introduced.

#### Enilconazole for veterinary use (1720)

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

**Impurities:** impurities A to F are now listed as specified impurities.

#### Ethyl parahydroxybenzoate (0900)

The revision has been agreed by the PDG (Pharmacopoeial Discussion Group) within the framework of international harmonisation.

**Identification:** identification D deleted because it is no longer relevant.

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

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

**Impurities:** impurity A is specified.

#### Eucalyptus oil (0390)

**Identification A:** a 2nd reference compound has been introduced to validate the separation and spacing between the zones in the TLC; the conditions for HPTLC have been added and the results are presented in the form of a table.

**Chromatographic profile:** in accordance with common practice the test solution and reference solutions are prepared using heptane as solvent; to take account of the changed concentration of the test solution, the split ratio and the injection volume have been adapted; a disregard limit has been introduced in accordance with chapter 2.2.46; peaks due to  $\alpha$ -pinene,  $\beta$ -pinene,  $\alpha$ -phellandrene and limonene are always present in the chromatogram obtained with the test solution (see Identification B) and a lower limit of content equal to the disregard limit has been introduced for those components; the upper limits of content for  $\alpha$ -pinene and limonene have been increased to include further geographical origins of the oil.

#### Filgrastim concentrated solution (2206)

**Related proteins:** a new method with better selectivity is introduced.

**Impurities with molecular masses differing from that of filgrastim:** reference solution (b), used in identification test D, has been added.

#### Flumequine (1517)

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

#### Folic acid (0067)

**Related substances:** preparation of reference solutions (b) and (e) changed; reagents used for quantification of impurities A and D replaced by corresponding CRSs according to current policy.

#### Foscarnet sodium hexahydrate (1520)

**Impurity D:** this impurity has been described as a CRS instead of a reagent.

**Related substances:** the injection volume has been increased; the use of *foscarnet impurity mixture CRS* and relative retentions of specified impurities have been introduced for peak identification; an explicit acceptance criterion for unspecified impurities has been introduced.

#### Fumitory (1869)

**Heavy metals:** a limit for cadmium different from the general requirement in the monograph *Herbal drugs (1433)* has been introduced.

#### Iceland moss (1439)

**Heavy metals:** a limit for lead different from the general requirement in the monograph *Herbal drugs (1433)* has been introduced.

#### Josamycin (1983)

**Identification:** in view of the replacement of the related substances TLC by LC, the TLC is now described under Identification; the coloured reaction has been deleted and a cross-reference to the related substances LC has been added.

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

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

#### Kaolin, heavy (0503)

**Substances soluble in mineral acids:** the title of this test has been revised to be more precise and accurate.

**Heavy metals:** the title of this test has been revised to be more precise and accurate.

#### Ketoprofen (0922)

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

#### Ketotifen hydrogen fumarate (1592)

**Related substances:**

- a change of the *impurity G CRS* standard implies changes in the preparation of reference solutions (b) and (c).
- the retention time of ketotifen has been included and relative retentions rounded to one decimal.
- the limit for any impurity has been replaced by a limit for the specified impurities and an explicit acceptance criterion for unspecified impurities has been introduced.

**Impurities:** impurities A to G are now listed as specified impurities.

#### Lavender oil (1338)

**Identification A:** cineole has been added as a 3rd reference substance; the conditions for HPTLC have been added.

**Optical rotation:** the range has been widened to include further geographical origins of the oil.

**Chromatographic profile:** in accordance with common practice the test and reference solutions are now prepared using heptane as solvent; to take account of the changed concentration of the solutions, the split ratio and the injection volume have been adapted; the upper limits of content for 3-octanone, linalyl acetate and terpinen-4-ol have been increased to include further geographical origins of the oil.

**Chiral purity:** the elution order has been added; it has been stated that the peaks due to borneol and (S)-linalol may elute in inversed order.

#### Lomustine (0928)

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

#### Lovastatin (1538)

**Related substances:** to assure the elution of impurity D within the described gradient the last step of the gradient has been prolonged.

#### Magnesium pidolate (1619)

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

#### Magnesium stearate (0229)

**Functionality-related characteristics:** particle-size distribution by laser light diffraction (the particle size would not allow analytical sieving) is considered useful for magnesium stearate used as a lubricant. This test will take into account changes in particle characteristics that might be introduced during the manufacturing process or resulting from the origin of stearic acid. Since this excipient is used in small quantities only, it was not considered useful to include a test for bulk and tapped density or for powder flow. The lubricant properties of magnesium stearate also depend on its water content and polymorphic form. A test for thermogravimetric analysis is therefore included to assess free and bound water.

#### Magnesium trisilicate (0403)

**Functionality-related characteristics (FRCs):** a section has been added; the following FRCs are considered useful for magnesium trisilicate used as a lubricant:

- particle-size distribution by laser light diffraction (the particle size would not allow analytical sieving);
- specific surface area.

These tests will take into account changes in particle characteristics that might be introduced during the manufacturing process.

#### Maprotiline hydrochloride (1237)

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

#### Marshmallow leaf (1856)

**Identification B:** illustration of powdered herbal drug added; description of pollen grains added.

#### Marshmallow root (1126)

**Identification B:** illustration of powdered herbal drug added. In this context, the detection of mucilage using ruthenium red solution has been added.

#### Meglumine (2055)

**Identification:** 2nd identification deleted; IR reference spectrum replaced by reference substance.

**Aluminium and Nickel:** tests added as meglumine is manufactured using Raney nickel as catalyst.

#### Methylene chloride (0932)

**Definition:** CAS number corrected.

**Identification C:** IR identification is now used.

**Related substances:** the test has been revised to cover volatile impurities in addition to the stabilisers. Heavy metals: the test has been revised to use the residue obtained under Residue on evaporation.

**Water:** method 2.5.12 replaced by method 2.5.32.

**Labelling:** the section has been added.

**Impurities:** specified impurities C and E deleted from the transparency list.

#### Methyl parahydroxybenzoate (0409)

The revision has been agreed by the PDG (Pharmacopoeial Discussion Group) within the framework of international harmonisation.

**Identification:** identification D deleted because it is no longer relevant.

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

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

**Impurities:** impurity A is specified.

#### Mupirocin calcium (1451)

**Assay:** clarification of the calculation.

#### Nabumetone (1350)

**Related substances:** explicit acceptance criterion introduced for unspecified impurities.

#### Omeprazole (0942)

**Identification:** 2nd identification deleted.

**Impurity C:** test deleted.

**Related substances:** LC modified to permit detection of impurity C; limits updated.

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

#### Oregano (1880)

**Identification B:** revised to allow differentiation between *O. onites* and *O. vulgare subsp. hirtum*; illustration of powdered drug added.

**Carvacrol and thymol:** hexane replaced by heptane as solvent.

#### Orphenadrine citrate (1759)

#### Orphenadrine hydrochloride (1760)

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

**Related substances:** relative retentions of specified impurities and the use of *orphenadrine for peak identification CRS* have been introduced for peak identification; an explicit acceptance criterion for unspecified impurities has been introduced; the disregard limit has been increased to 0.05 per cent.

**Impurities:** the impurities A to F are now listed as specified impurities.

#### Oxybutynin hydrochloride (1354)

**Identification B:** sample preparation deleted.

**Related substances:** explicit acceptance criterion introduced for unspecified impurities; the disregard limit has been increased to 0.05 per cent in accordance with current policy; in the mobile phase, *acetonitrile R* has been replaced by *acetonitrile RI*.

#### Potassium clavulanate (1140)

#### Potassium clavulanate, diluted (1653)

**Related substances:** as the content of impurity E in *potassium clavulanate for impurity E identification CRS* decreases rapidly, this CRS is not suitable for the identification of impurity E; identification of impurity E is now carried out via the relative retention.

#### Prochlorperazine maleate (0244)

**Identification C:** chloroform has been replaced by methylene chloride.

**Loss on drying:** the precision of the quantity used has been increased.

#### **Propyl parahydroxybenzoate (0431)**

The revision has been agreed by the PDG (Pharmacopoeial Discussion Group) within the framework of international harmonisation.

**Identification:** identification D deleted because it is no longer relevant.

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

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

**Impurities:** impurity A is specified.

#### **Salbutamol sulphate (0687)**

**Characters:** it has been added that the substance shows polymorphism.

**Identification by IR:** description of the sample preparation deleted in accordance with current policy; recrystallisation procedure, related to polymorphism has been added.

**Related substances:** the LC method has been replaced by one which is suitable for substances from several sources and is able to control additional impurities including impurity J which was formerly covered by a separate photometric test; impurity H has been deleted as it was not relevant for the sources of salbutamol sulphate which form the basis of this monograph; limits based on current batch data.

**Impurities:** specified impurities N and O and other detectable impurities K, L and M have been added.

#### **Sodium methyl parahydroxybenzoate (1262)**

**Definition:** the lower limit for content has been decreased as an LC assay is now prescribed.

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

**Identification:** test A has been deleted in the 1st identification; test D has been deleted in the 2nd identification.

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

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

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

**Impurities:** impurity A is specified.

#### **Sodium stearyl fumarate (1567)**

**Functionality-related characteristics (FRCs):** a section has been added; the following FRCs are considered useful for sodium stearyl fumarate used as a lubricant:

- particle-size distribution by laser light diffraction (the particle size would not allow analytical sieving);
- specific surface area.

These tests will take into account changes in particle characteristics that might be introduced during the manufacturing process.

#### **Soya-bean oil, hydrogenated (1265)**

**Definition:** the wild species is no longer used for the production of the oil.

**Water:** hydrogenated oils are obtained from oils which are hydrogenated at 200 °C, bleached at 90 °C under a very low pressure then deodorised at a temperature greater than 190 °C under a pressure of about 5 mm

Hg. As a consequence, the resulting water content is negligible and it is not considered pertinent to guarantee the quality of this oil. Microbial growth is very unlikely to occur on such a substrate.

#### **Stearic acid (1474)**

**Functionality-related characteristics (FRCs):** a section has been added; the following FRCs are considered useful for stearic acid used as a lubricant:

- particle-size distribution by laser light diffraction (the particle size would not allow analytical sieving);
- specific surface area.

These tests will take into account changes in particle characteristics that might be introduced during the manufacturing process.

#### **Theophylline-ethylenediamine, anhydrous (0300)**

**Heavy metals:** reference to method H has been included.

**Water:** the test has been modified to avoid the use of pyridine.

#### **Theophylline-ethylenediamine hydrate (0301)**

**Definition:** chemical formula, molecular formula, molecular mass and CAS number have been modified.

**Heavy metals:** reference to method H has been included.

**Water:** the test has been modified to avoid the use of pyridine.

#### **Tormentil (1478)**

**Heavy metals:** a limit for cadmium that is different from the general requirement in the monograph *Herbal drugs (1433)* has been introduced.

#### **Tri-n-butyl phosphate (1682)**

**Related substances:** based on batch data, the limit for any impurity has been widened to 0.3 per cent and the total to 0.5 per cent.

#### **Trolamine (1577)**

**Impurity C:** GC-MS method replaced by a more robust method.

**Related substances:** the reagents used for impurities A and B have been replaced by CRSs and the amount used has been decreased.

#### **Valerian dry aqueous extract (2400)**

**Assay:** *valerian standardised dry extract CRS* has been replaced by *valerian dry extract HRS*; to assure the elution of valerenic acid within the described gradient the last step of the gradient has been prolonged.

#### **Valerian root (0453)**

**Definition:** the references to the cut drug have been deleted since it is now covered by the monograph *Cut valerian root (2526)*.

**Identification C:** HPTLC conditions have been added.

**Assay:** *valerian standardised dry extract CRS* has been replaced by *valerian dry extract HRS*; the last step of the gradient has been prolonged to ensure the elution of valerenic acid within the described gradient.

#### **Valerian tincture (1899)**

**Identification:** the size of the bands has been specified for the application.

**Assay:** *valerian standardised dry extract CRS* has been replaced by *valerian dry extract HRS*; to assure the elution of valerenic acid within the described gradient the last step of the gradient has been prolonged.

#### **Willow bark (1583)**

**Heavy metals:** a limit for cadmium that is different from

the general requirement in the monograph *Herbal drugs (1433)* has been introduced.

**Xylazine hydrochloride for veterinary use (1481)**

**Identification A:** the method of sample preparation is no longer specified according to the current policy.

**Related substances:** *xylazine impurity mixture CRS* has been introduced for peak identification of specified impurities B and D.

**Yarrow (1382)**

**Identification B:** illustration of the powdered herbal drug added.

**Zinc acexamate (1279)**

**Identification A:** the method of sample preparation is no longer specified according to current policy.

**Related substances:** an explicit acceptance criterion for unspecified impurities has been introduced.