

COMMENTS CONCERNING SOME REVISED/CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 6.4

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

GENERAL TEXTS

2.2.46. Chromatographic separation techniques

A general revision of the chapter has been undertaken in light of several years' experience. Major changes are as follows.

Definitions. IUPAC terminology has been used wherever possible. Additional definitions have been introduced in particular for size-exclusion chromatography parameters and for dwell volume (together with a method for its determination). For the signal-to-noise ratio, the observation window for the baseline has been reduced to a distance equal to 5 times the width at half-height of the peak, to cover short-term noise only.

System suitability. It has been clarified that the requirement for peak symmetry of 0.8-1.5 applies to a peak in the chromatogram obtained with a reference solution used for quantification and that the repeatability requirements only apply to active substances where the theoretical value for a pure substance is 100 per cent. The requirement for the limit of detection has been deleted; it is redundant, since compliance with the limit of quantitation is required. Compliance with the system suitability criteria throughout the chromatographic procedure has been required.

Adjustment of chromatographic conditions. Isocratic and gradient elutions in liquid chromatography are now dealt with separately; for both, a formula has been added for adjustment of flow rate where a column with different dimensions from those prescribed is used and the permitted adjustment for column temperature is now expressed more meaningfully in absolute terms ($\pm 10\text{ }^{\circ}\text{C}$ for isocratic and $\pm 5\text{ }^{\circ}\text{C}$ for gradient elution) rather than as a percentage. For gradient elutions, only minor adjustments are possible. The gradient point times can be adapted to take account of differences in dwell volume between the system used during the elaboration of the method and the one actually used, when there is an isocratic step.

3.1.11. Materials based on non-plasticised poly(vinyl chloride) for containers for dry dosage forms for oral administration

Absorbance of solution S2: the test serves inter alia to control the tin content, but the limit of 0.5 for absorbance is incompatible with the maximum allowed content of tin-containing stabiliser; the limit is therefore raised to 1.0.

VACCINES FOR HUMAN USE

Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) (2149)

Influenza vaccine (whole virion, inactivated, prepared in cell cultures) (2308)

Extraneous agents: the duration of the testing described in chapter 2.6.16 is not always compatible with the timely availability of vaccine, so the use of rapid assays (e.g. PCR), to be applied in parallel with chapter 2.6.16, has been introduced; the use of PCR is only allowed in a well-defined context (validation for the specific vaccine together with risk assessment approach).

Typhoid vaccine (live, oral, strain Ty 21a) (1055)

Final bulk vaccine: the requirement to aseptically prepare the final bulk has been deleted and replaced by preparation under suitable conditions.

Final lot: the requirement to aseptically prepare the final lot has been deleted and replaced by preparation under suitable conditions.

The changes are in line with currently marketed products.

MONOGRAPHS

Acetazolamide (0454)

Characters: a statement of the occurrence of polymorphism has been added.

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

Related substances: TLC has been replaced by LC in accordance with current policy. Impurities: a section describing the impurities controlled by the LC test has been added.

Amlodipine besilate (1491)

Identification: second series is not of practical relevance for this substance and has therefore been deleted.

Related substances: the TLC and LC have been replaced by a single LC, which covers the previously mentioned impurities except impurity C. Impurity C seems to be a theoretical impurity: it has never been obtained, nor has it been detected in any of the batches from different producers. The new method also allows the detection of

4 additional impurities. Water: sample weight has been reduced to 1.000 g.

Atenolol (0703)

Related substances: the LC method has been revised to obtain separation of the new specified impurity I; the limits for individual impurities have been reduced from the previous limit of 0.25 per cent, based on current batch data.

Impurities: the impurities have been classified as Specified impurities or Other detectable impurities, according to the limits proposed; impurity C is not present in the batches and has been deleted from the list.

Benserazide hydrochloride (1173)

Identification A: method of sample preparation no longer specified.

Optical rotation: test deleted because optical rotation values of pure enantiomers not known.

Related substances: LC method replaced by one giving better separation of impurities.

Impurities: impurities A, B and C specified.

Bentonite (0467)

Identification: swelling power with water has been maintained to differentiate bentonite from heavy kaolin, but a cross-reference to this identification test has been included in the FRC section.

Functionality-related characteristics: bentonite is used as viscosity-increasing agent in oral and cutaneous preparations. It is also a suspending agent. It has been decided to keep the test for coarse particles in the mandatory part of the monograph. The test for sedimentation volume, including typical values, has been moved to the FRC section. Although the 2 tests of the FRC section appear to be outdated, it has not been possible to find more recent ones.

Benzalkonium chloride (0372)

Definition: the definition has been revised to show that the content is now calculated on the basis of the average relative molecular mass of the sample.

Identification: a new test has been introduced to use the LC procedure of the test for average relative molecular mass and ratio of alkyl components. In test D chloroform has been replaced by methylene chloride.

Average relative molecular mass and ratio of alkyl components: an LC procedure has been introduced with limits for C₁₂ and C₁₄ homologues.

Impurities A, B and C: an LC procedure has been introduced with specified limits for benzyl alcohol, benzaldehyde and benzyl chloride based on current batch data.

Assay: chloroform has been replaced by methylene chloride; the assay calculation has been revised to take account of the average relative molecular mass of the sample.

Storage: as the substance is hygroscopic, storage in an airtight container has been added.

Benzalkonium chloride solution (0371)

Definition: the definition has been revised to show that the content is now calculated on the basis of the average relative molecular mass of the sample.

Identification: a new test has been introduced to use the LC procedure of the test for average relative molecular

mass and ratio of alkyl components. In test D chloroform has been replaced by methylene chloride.

Average relative molecular mass and ratio of alkyl components: an LC procedure has been introduced with limits for C₁₂ and C₁₄ homologues.

Impurities A, B and C: an LC procedure has been introduced with specified limits for benzyl alcohol, benzaldehyde and benzyl chloride based on current batch data.

Assay: chloroform has been replaced by methylene chloride; the assay calculation has been revised to take account of the average relative molecular mass of the sample.

Calcium hydrogen phosphate, anhydrous (0981)

Functionality-related characteristics: this section has been added. Anhydrous calcium hydrogen phosphate is widely used as filler in tablet and capsule formulations. Tests typically retained for fillers are therefore included: particle-size distribution and powder flow. Since this excipient is used in large quantities, it was also useful to include a test for bulk and tapped density.

Calcium hydrogen phosphate dihydrate (0116)

Solubility: cold water has been replaced by water.

Functionality-related characteristics: this section has been added. Calcium hydrogen phosphate dihydrate is widely used as filler in tablet and capsule formulations. Tests typically retained for fillers are therefore included: particle-size distribution and powder flow. Since this excipient is used in large quantities, it is also useful to include a test for bulk and tapped density.

Calcium phosphate (1052)

Functionality-related characteristics: this section has been added. Calcium phosphate is widely used as filler in tablets and capsules. Tests typically retained for fillers are therefore included: particle-size distribution and powder flow. Since this excipient is used in large quantities, it is also useful to include a test for bulk and tapped density.

Calcium sulphate dihydrate (0982)

Functionality-related characteristics: this section has been added. Calcium sulphate dihydrate is widely used as filler in tablet and capsule formulations. Tests typically retained for fillers are therefore included: particle-size distribution and powder flow. Since this excipient is used in large quantities it is also useful to include a test for bulk and tapped density.

Carbomers (1299)

Functionality-related characteristics: this section has been added. Carbomers are mainly used as viscosity-increasing agents and gelling agents. In addition to the test for apparent viscosity, which has been moved from the section Tests, the assay of carboxylic acid groups has been added in order to trace any substitution of the carboxylic acid groups, which could influence viscosity. **Identification/Labelling:** reference to the nominal apparent viscosity has been deleted.

Cyclopentolate hydrochloride (1093)

Characters: statement added on occurrence of polymorphism.

Identification C: TLC test previously also used for related substances adapted.

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

Impurities: section added describing impurities controlled by LC.

Dextrin (1507)

Functionality-related characteristics: this section has been added. Dextrin is used as filler and as binder for wet granulation, as thickening agent in suspension and as adhesive and thickening agent in surgical adhesives. The test for reducing sugars was envisaged as an FRC, but this idea was not retained because the low glucose contamination permitted by this test will not have an impact on the viscosity and the binding properties. It has been decided to mention the use of dextrin as filler, binder and viscosity-increasing agent. Particle-size distribution, powder flow and apparent viscosity are therefore included.

Diflunisal (0818)

Characters: a statement of the occurrence of polymorphism has been added.

Identification B: according to the current policy the sample preparation method is no longer specified.

Dihydroergotamine mesilate (0551)

Related substances: impurity E reclassified as a specified impurity with a limit of 0.5 per cent, based on current batch data.

Doxepin hydrochloride (1096)

Heavy metals: method D has been replaced by method A.

Glucose, liquid, spray-dried (1525)

Functionality-related characteristics: this section has been added. Spray-dried liquid glucose is mainly used as filler or binder for wet granulation. A test typically retained for fillers and binders has been included: particle-size distribution. Powder flow, however, is not added because this excipient does not flow easily. Since the degree of hydrolysis may influence the functionality, a cross-reference to the Dextrose equivalent test has been included.

Hawthorn leaf and flower dry extract (1865)

Methanol: the test has been deleted since a requirement on residual solvents has been introduced into the general monograph Extracts (0765).

Heparin calcium (0332)

Heparin sodium (0333)

The following revised monograph was adopted by the European Pharmacopoeia Commission at its 131st session, on 25 June 2008, using the rapid implementation procedure. The implementation date is 1 August 2008.

Production. At its 130th session (March 2008), the European Pharmacopoeia Commission requested the Expert Group in charge of biological substances to look into the heparin monographs and see how best to deal with the present contamination concerns. In addition to the Group's meeting in April 2008, *ad hoc* meetings and a workshop were held with interested parties to gather in-depth and up-to-date knowledge of the situation and help define a strategy for revision.

Control of over-sulphated chondroitin sulphate had to be urgently addressed. A link has now been established between this contaminant and the occurrence of serious hypotensive and allergic reactions such as those observed in certain patients. The revision deals with the need for a requirement to screen heparin batches systematically for absence of this contaminant while acknowledging that the screening methods could later be improved or replaced. Further progress is also yet to be made in the understanding of how toxicity is induced in man and what levels of the contaminant trigger the adverse reactions. The absence of a suitable, established reference standard to be used with these methods has also been considered. The importance of sourcing and the absence of mixes of crude heparins from different species of origin are highlighted.

In addition to this emergency measure, it is the Expert Group's intention to carry out longer-term revision work and introduce a comprehensive set of tests allowing to detect naturally occurring contaminants such as dermatan sulphate, and to limit such process-related substances.

Low-molecular-mass heparins are covered as well since the monograph *Low-molecular-mass heparins (0828)* states that they are obtained from heparin of natural origin that complies with the monograph *Heparin sodium (0333)* or *Heparin calcium (0332)*, whichever is appropriate. This applies to all low-molecular-mass heparins, whether a specific Ph. Eur. monograph exists (*Dalteparin sodium (1195)*, *Enoxaparin sodium (1097)*, *Nadroparin calcium (1134)*, *Parnaparin sodium (1252)*, *Tinzaparin sodium (1271)*) or not.

Labelling. A statement on the suitability of the substance for use in the manufacture of parenteral preparations has been added, according to current policy. The statement on added substances has been deleted since it is covered by the general monograph *Substances for pharmaceutical use (2034)*.

Hydrochlorothiazide (0394)

Characters: the substance shows polymorphism.

Hydrocodone hydrogen tartrate 2.5-hydrate (1784)

Related substances: impurity A (morphine) in the current CRS for peak identification has partially degraded, whereas the chromatogram remained unchanged for the other specified impurities. Therefore, a separate reference solution containing morphine sulphate has been introduced for identification of impurity A.

Itraconazole (1335)

Definition: content limits have been tightened based on current batch data.

Identification: deletion of the second series to avoid the use of dioxan.

Appearance of solution: based on current batch data, the best matches for the colour are red or brown reference solutions, hence "BY₆" is changed to "R₆ or B₆".

Optical rotation: the test has been deleted since it does not give additional information.

Related substances: LC conditions have been optimised to achieve a better separation (addition of an isocratic step, temperature); *itraconazole for system suitability CRS* has been introduced to allow the identification of impurities; limits have been tightened

based on current batch data; a classification of impurities has been added, in which impurities A and F are classified as Other detectable impurities.

Assay: a vigorous agitation is necessary to dissolve the sample and this has been specified.

Java tea (1229)

Identification B: illustration of the powdered herbal drug added.

Levamisole hydrochloride (0726)

Related substances: *levamisole hydrochloride for system suitability CRS* is used for identification of impurities; a higher value than the one specified in chapter 2.2.46 is acceptable for peak symmetry.

Impurities: impurities A to E are listed as specified impurities.

Magnesium carbonate, light (0042)

Functionality-related characteristics: this section has been added. Light magnesium carbonate is used as filler in oral solid dosage forms. Tests typically retained for fillers are therefore included: particle-size distribution is included but powder flow is not, because this excipient does not flow easily; bulk and tapped density is useful to differentiate it from the heavy grade of magnesium carbonate.

Magnesium citrate, anhydrous (2339)

Appearance of solution: anhydrous magnesium citrate may contain small amounts (500 ppm) of nonhydrate (practically insoluble in water), either from the manufacturing process or as a result of uptake of traces of humidity during storage; the limit has been widened.

Magnesium oxide, heavy (0041)

Functionality-related characteristics: this section has been added. Heavy magnesium oxide is widely used as filler in oral solid dosage forms. Tests typically retained for fillers are therefore included: particle-size distribution is included but powder flow is not, because this excipient does not flow easily; bulk and tapped density is useful to differentiate it from the light grade of magnesium oxide.

Magnesium oxide, light (0040)

Functionality-related characteristics: this section has been added. Light magnesium oxide is used as filler in oral solid dosage forms. Tests typically retained for fillers are included: particle-size distribution is included but powder flow is not, because this excipient does not flow easily; bulk and tapped density is useful to differentiate it from the heavy grade of magnesium oxide.

Maltodextrin (1542)

Functionality-related characteristics: this section has been added. Maltodextrin is mainly used as tablet filler and as binder both for wet granulation and direct compression. Tests typically retained for fillers and binders are included: particle-size distribution and powder flow. Since the degree of hydrolysis may influence the functionality, a cross-reference to the test Dextrose equivalent has been included.

Mannitol (0559)

Functionality-related characteristics: this section has been added. Mannitol is mainly used as filler in tablets

prepared by wet granulation or by direct compression. Tests typically retained for fillers are therefore included: particle-size distribution and powder flow.

Melissa leaf (1447)

Content: limit adapted to new assay method.

Identification A: botanical description improved.

Identification B: illustration of powdered herbal drug introduced.

Identification C: conditions for HPTLC added.

Assay: UV spectrophotometric assay replaced by more specific LC assay on rosmarinic acid.

Phenytoin (1253)

Identification: the second series has been deleted to avoid the use of toxic reagents and because the substance is not used in pharmacies.

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

Impurities: addition of specified impurities C, D and E and other detectable impurity F.

Phenytoin sodium (0521)

Identification A: chloroform has been replaced by the less toxic solvent ethyl acetate.

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

Impurities: addition of a section describing the impurities controlled by the LC.

Simvastatin (1563)

Identification B: the method of sample preparation is not specified, according to current policy.

Related substances: the same test solution is now used for both the test for related substances and the assay; a new reference solution (d) has been added in order to identify impurities A, B, C, D, E, F and G; a limit for unspecified impurities has been introduced.

Storage: the storage recommendation "under nitrogen, in an airtight container" has been restricted to cases where no antioxidant is used.

Labelling: the section has been deleted because this information is already included in the general monograph *Substances for pharmaceutical use (2034)*.

Impurity G: the formula has been corrected.

Sorbitol (0435)

Functionality-related characteristics: this section has been added. Sorbitol is mainly used as filler and binder in tablet formulations prepared by wet granulation or direct compression. Tests typically retained for fillers and binders are therefore included: particle-size distribution and powder flow.

Thyme (0865)

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

Xanthan gum (1277)

Functionality-related characteristics: this section has been added. Xanthan gum is mainly used as viscosity-increasing agent but also as matrix former in prolonged-release tablets. For the 1st case, apparent viscosity has been added; for the 2nd case, apparent viscosity, particle-size distribution and powder flow have been added.