

## Comments concerning revised texts published in Supplement 9.5

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the June 2017 session and published in Supplement 9.5.

When a text has been technically revised, this is indicated by horizontal or vertical lines in the margin of the supplement. The details given below complete this information, but are not necessarily exhaustive.

The following details can also be consulted in the [Knowledge database](#) under View history.

### GENERAL CHAPTERS

#### 2.2.7. Optical rotation

Equipment description added to the chapter. Clarifications in the description of the analytical procedure and the equipment performance introduced.

#### 2.4.20. Determination of elemental impurities

Addition of a reference to *elemental impurity solutions CRS*.

#### 3.2.9. Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders

The scope of this general chapter has been expanded to include coated closures, bi-layer seals and lubricated closures to reflect better the range of closures on the market. More details are provided in the Identification section for greater clarity.

**Identification A** (IR spectrophotometry): the amount of rubber required is described as 'an appropriate amount' to allow more flexibility.

**Identification B** (total ash): a precision has been added on how to proceed with samples that are not subjected to steam sterilisation; an indication has been added to allow compliance with the limit for a specific rubber type, when a type sample is not available.

**Solution S**: the washing step performed before the preparation of solution S has been deleted; the procedure for the measurement of the temperature during autoclaving has been clarified.

**Appearance of solution S**: limits for nephelometric measurements have been included.

**Acidity or alkalinity**: clarification has been added on when to perform the titration.

**Extractable zinc**: the description of the test solution preparation is now more specific.

**Self-sealing test**: a requirement to use a vial that fits with the closure has been added.

#### 4.1. Reagents, standard solutions, buffer solutions

The requirement to use *water for chromatography R* during the preparation of aqueous mobile phases in liquid chromatography has been added.

#### 5.4. Residual solvents

Aligned to the latest version of the ICH Guideline Q3C (R6): the permitted daily exposure limit for methylisobutylketone is lowered to 45.0 mg/day (i.e. change from Class 3 to Class 2); triethylamine is a new Class 3 solvent.

#### 5.12. Reference standards

**Terminology:** in the definition of CRSs, the paragraph referring to ISO Guide 34 has been deleted.

## GENERAL MONOGRAPHS

### Pharmaceutical preparations (2619)

**Definition:** reference to 2 homoeopathic dosage form monographs *Homoeopathic pillules, coated (2786)* and *Homoeopathic pillules, impregnated (2079)* introduced.

### Vaccines for human use (0153)

**Animal tests:** a cross-reference to general chapter 5.2.14. *Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines* has been introduced.

### Vaccines for veterinary use (0062)

**Animal tests:** a cross-reference to general chapter 5.2.14. *Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines* has been introduced.

## VACCINES FOR HUMAN USE

### Diphtheria, tetanus, pertussis (acellular, component) and haemophilus type b conjugate vaccine (adsorbed) (1932)

**General provisions:** tests in animals are no longer regarded as sufficient to monitor the quality of the vaccine, whereas physico-chemical tests have become more pertinent and discriminating for demonstrating that the conjugate has not been affected by a change in the manufacturing process. It is therefore no longer indispensable to resort to an animal model each time the manufacturing process is changed and the text has been updated accordingly.

### Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2067)

**General provisions:** tests in animals are no longer regarded as sufficient to monitor the quality of the vaccine, whereas physico-chemical tests have become more pertinent and

discriminating for demonstrating that the conjugate has not been affected by a change in the manufacturing process. It is therefore no longer indispensable to resort to an animal model each time the manufacturing process is changed and the text has been updated accordingly.

#### **Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2065)**

**General provisions:** tests in animals are no longer regarded as sufficient to monitor the quality of the vaccine, whereas physico-chemical tests have become more pertinent and discriminating for demonstrating that the conjugate has not been affected by a change in the manufacturing process. It is therefore no longer indispensable to resort to an animal model each time the manufacturing process is changed and the text has been updated accordingly.

#### **Diphtheria, tetanus, pertussis (whole cell), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2066)**

**General provisions:** tests in animals are no longer regarded as sufficient to monitor the quality of the vaccine, whereas physico-chemical tests have become more pertinent and discriminating for demonstrating that the conjugate has not been affected by a change in the manufacturing process. It is therefore no longer indispensable to resort to an animal model each time the manufacturing process is changed and the text has been updated accordingly.

#### **Haemophilus type b conjugate vaccine (1219)**

**General provisions:** tests in animals are no longer regarded as sufficient to monitor the quality of the vaccine, whereas physico-chemical tests have become more pertinent and discriminating for demonstrating that the conjugate has not been affected by a change in the manufacturing process. It is therefore no longer indispensable to resort to an animal model each time the manufacturing process is changed and the text has been updated accordingly.

## SUTURES FOR HUMAN USE

#### **Sutures, sterile non-absorbable (0324)**

**Definition:** the scope has been widened to take also into account sutures composed of blends of materials cited in the monograph.

**Identification:** IR using attenuated total reflection (ATR) (2.2.24) is now prescribed for various materials, replacing tests using hazardous chemicals and tests using previous IR methods; the main peaks are given with an indication of their intensity (strong, medium, weak); the identification sections for polyamide 6 and polyamide 6/6 have been merged as they give similar results.

## SUTURES FOR VETERINARY USE

#### **Polyamide 6 suture, sterile, in distributor for veterinary use (0609)**

**Definition:** the scope has been widened to take also into account sutures composed of blends of polyamide 6 and polyamide 6/6.

**Identification:** to prevent the use of hazardous chemicals, identification is no longer performed by chemical tests, which are replaced by IR using attenuated total reflection (ATR) (2.2.24); the main peaks are given with an indication of their intensity (strong, medium, weak).

#### **Polyamide 6/6 suture, sterile, in distributor for veterinary use (0610)**

**Definition:** the scope has been widened to take also into account sutures composed of blends of polyamide 6/6 and polyamide 6.

**Identification:** to prevent the use of hazardous chemicals, identification is no longer performed by chemical tests, which are replaced by IR using attenuated total reflection (ATR) (2.2.24); the main peaks are given with an indication of their intensity (strong, medium, weak).

#### **Poly(ethylene terephthalate) suture, sterile, in distributor for veterinary use (0607)**

**Identification:** to prevent the use of hazardous chemicals, identification is no longer performed by chemical tests, which are replaced by IR using attenuated total reflection (ATR) (2.2.24); the main peaks are given with an indication of their intensity (strong, medium, weak).

## HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

#### **Lavender flower (1534)**

**Characters:** section deleted.

**Identification C:** TLC replaced by cross-reference to HPTLC test for lavandin flower and results table introduced.

**Tests:** HPTLC test for lavandin flower introduced; hexane replaced by heptane in the test for other species and varieties of lavender.

#### **Lavender oil (1338)**

**Identification A:** TLC/HPTLC method updated.

**Chromatographic profile:** reagents used in reference solution (a) replaced by *lavender oil for peak identification HRS*.

#### **Spike lavender oil (2419)**

**Identification A:** TLC/HPTLC method updated.

## HOMOEOPATHIC PREPARATIONS

#### **Agaricus phalloides for homoeopathic preparations (2290)**

**Identification A (mother tincture):** addition of HPTLC conditions.

#### **Arsenicum album for homoeopathic preparations (1599)**

**Appearance of solution:** preparation of solution modified to ensure dissolution of the substance in *dilute ammonia R1*.

## Aurum chloratum natronatum for homoeopathic preparations (2141)

**CAS number:** added.

**Nitrates:** test improved; oxalic acid replaced by a solution of zinc and dilute sulfuric acid.

# MONOGRAPHS

## Acitretin (1385)

**Identification:** 2<sup>nd</sup> series deleted as substance not used in pharmacies for extemporaneous preparations.

**Related substances:** LC updated and explicit criterion for unspecified impurities introduced in accordance with current policy.

**Palladium:** test deleted in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities.

**Impurities:** section updated.

## Biotin (1073)

**Identification C:** test deleted.

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

**Impurities:** section updated and impurity C corrected.

## Codeine hydrochloride dihydrate (1412)

**Identification:** IR reference spectrum replaced by CRS in identification test A; reference to test for water introduced as identification test F.

**Related substances:** UHPLC method covering additional impurities now used.

**Impurities:** section updated.

## Codeine monohydrate (0076)

**Title:** degree of hydration specified.

**Identification:** IR sample preparation deleted in accordance with current policy; reference to test for loss on drying introduced as identification test F.

**Related substances:** UHPLC method covering additional impurities now used.

**Assay:** colour indicator replaced by potentiometric end-point determination.

**Impurities:** section updated.

## Codeine phosphate hemihydrate (0074)

**Content:** lower limit increased.

**Identification B:** reference spectrum replaced by CRS.

**Related substances:** UHPLC method covering additional impurities now used.

**Assay:** colour indicator replaced by potentiometric end-point determination.

**Impurities:** section updated.

### Estriol (1203)

**Content:** limits updated to reflect change of assay method.

**Characters:** melting point deleted.

**Identification:** TLC replaced by a cross-reference to LC for assay.

**Related substances:** more robust method introduced, which allows for the control of additional impurities.

**Assay:** UV absorbance replaced by modified LC for related substances.

### Folic acid hydrate (0067)

**Title and Definition:** updated to include degree of hydration.

**Identification B:** LC replaced by IR.

**Identification D:** cross-reference to the test for water introduced.

**Related substances:** limits updated; new specified impurities added and system suitability updated accordingly; run time extended to cover possible impurities due to improper storage.

**Storage:** updated to avoid formation of oxidation products.

### Gemfibrozil (1694)

**Assay:** volumes of solvents used to dissolve substance to be examined modified.

**Related substances:** grade of solvent amended in accordance with the Technical Guide (2015).

### Glucosamine hydrochloride (2446)

**Related substances:** the CRS for system suitability was prepared by lyophilisation, therefore it was necessary to revise the preparation of reference solution (b); reagent used to describe stationary phase modified.

### Glucosamine sulfate potassium chloride (2708)

**Related substances:** the CRS for system suitability was prepared by lyophilisation, therefore it was necessary to revise the preparation of reference solution (b); reagent used to describe stationary phase modified.

### Glucosamine sulfate sodium chloride (2447)

**Related substances:** the CRS for system suitability was prepared by lyophilisation, therefore it was necessary to revise the preparation of reference solution (b); reagent used to describe stationary phase modified.

### Hydroxypropylcellulose, low-substituted (2083)

**Functionality-related characteristics (FRCs):** section added for low-substituted hydroxypropylcellulose used as disintegrant; settling volume, degree of substitution and particle-size distribution added as FRCs.

### Hyoscine butylbromide (0737)

**pH:** test replaced by test for acidity or alkalinity.

**Related substances:** method improved and specifications updated.

### Insulin glargine (2571)

**Peptide mapping:** information about peaks to be identified for system suitability test updated.

**Impurities with molecular masses greater than that of insulin glargine:** improved method using a single chromatographic column now described.

Grades of solvents amended in accordance with the Technical Guide (2015).

### Isoniazid (0146)

**Impurity E, Related substances:** TLC test for hydrazine and related substances replaced by LC test for impurity E (hydrazine) and LC test for related substances, which covers impurities A, B, C and D.

**Impurities:** section introduced.

### Isotretinoin (1019)

**Identification:** 2<sup>nd</sup> identification series deleted as substance not used in pharmacies for extemporaneous preparations.

**Related substances:** impurities H and I no longer specified; limits have been updated.

### Lactulose (1230)

**Assay:** introduction of a less-strict criterion for symmetry factor than that indicated in 2.2.46. *Chromatographic separation techniques.*

### Lactulose, liquid (0924)

**Identification A:** accuracy of mass and volume increased; more-common TLC plate described.

**Assay:** introduction of a less-strict criterion for symmetry factor than that indicated in 2.2.46. *Chromatographic separation techniques.*

### Mometasone furoate (1449)

**Content:** limits updated to reflect change of assay method.

**Characters:** melting point deleted.

**Identification:** IR sample preparation deleted in accordance with current policy; in 1<sup>st</sup> identification series TLC replaced by cross-reference to LC assay, and cross-reference to loss on drying introduced.

**Related substances:** LC modified to allow control of additional impurities, and limits updated.

**Assay:** LC for related substances now used.

**Impurities:** section updated.

### Neostigmine metilsulfate (0626)

**Related substances:** reporting threshold clarified with respect to impurity B; *acetonitrile for chromatography R* now indicated for the mobile phase.

### Paraffin, light liquid (0240)

**Functionality-related characteristics (FRCs):** section added for light liquid paraffin used as emollient in ointments, as vehicle in eye preparations or as lubricant in tablets and capsules; cross-reference to test for viscosity added.

### Paraffin, liquid (0239)

**Functionality-related characteristics (FRCs):** section added for liquid paraffin used as emollient in ointments, as vehicle in eye preparations or as lubricant in tablets and capsules; cross-reference to test for viscosity added.

### Pimobendan for veterinary use (2179)

**Title, Related substances:** as the substance is for veterinary use only, the title of the monograph has been modified and the limits have been revised in accordance with general monograph *Substances for pharmaceutical use (2034)*.

### Polyoxypropylene stearyl ether (2602)

**Functionality-related characteristics (FRCs):** section added for polyoxypropylene stearyl ether used as solvent or emollient in preparations for cutaneous application; cross-reference to identification test for viscosity added.

### Sevoflurane (2269)

**Related substances:** *sevoflurane CRS* replaced by *sevoflurane for system suitability CRS* (containing impurities A and B).