

## Comments concerning revised texts published in Supplement 10.3

*The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November 2019 session and published in Supplement 10.3.*

*When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.3. 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

#### 2.2.2. Degree of coloration of liquids

Inclusion of the instrumental method as harmonised by the PDG (revised signed-off text dated 27 June 2019). Editorial changes in the visual method.

#### 2.2.24. Absorption spectrophotometry, infrared

**Principles:** clarification of the text.

**Procedure - Transmission mode:** more flexibility is given with regard to the minimum transmittance requirement.

#### 2.2.29. Liquid chromatography

**Principle:** more accuracy given for the size of reduced-particle size columns.

**Stationary phases column temperature:** deletion of “room temperature” to avoid misunderstanding regarding the temperature adjustment allowed in the context of chapter 2.2.46.

#### 2.2.38. Conductivity

This general chapter has been revised within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia:

- correction of the PAT nomenclature,
- clarifications are made on the temperature compensations applied to water.

### 2.2.49. Falling ball and automatic rolling ball viscometer methods

**Method A:** repeatability requirements improved.

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

**4-5-1. Preparation of the sample:** sample preparation for orodispersible films added.

**5-1. Amount used for the test:** number of orodispersible films to be sampled specified.

General chapters 2.6.13 and 5.1.4 have been revised to include provisions for addressing the microbiological quality of orodispersible films, published in the same supplement.

These requirements for orodispersible films apply in the Ph. Eur. as local requirements.

### 2.6.13. Microbiological examination of non-sterile products: test for specified micro-organisms

**Sample preparation and pre-incubation:** sample preparation for testing orodispersible films for *Escherichia coli* (4-2-1), *Pseudomonas aeruginosa* (4-4-1) and *Staphylococcus aureus* (4-5-1) have been added.

General chapters 2.6.12 and 5.1.4 have been revised to include provisions for addressing the microbiological quality of orodispersible films and are published in the same supplement.

These requirements for orodispersible films apply in the Ph. Eur. as local requirements.

### 2.6.27. Microbiological examination of cell-based preparations

A clarification has been carried out in section 3-1-2. Method suitability.

This section has been modified to avoid confusion between 'validation' and 'confirmation of the suitability of the method' for the automated growth-based method. The critical parameters described are to be verified as part of confirmation of method suitability.

### 2.7.14. Assay of hepatitis A vaccine

**Method A. In vitro assay.** The detailed standard operating procedure for the ELISA method, which was given as an example of a suitable immunochemical method for determination of the antigen content, has been deleted further to the discontinuation of the associated biological reference reagents (BRRs).

The ELISA method previously given as an example was based on the outcome of a collaborative study 'Validation of a new ELISA method for *in vitro* potency testing of hepatitis A vaccines' published in Pharmeuropa Bio & Scientific Notes in 2013, the results of which may be of interest to users wishing to establish a similar assay with self-qualified reagents.

### 2.9.19. Particulate contamination: sub-visible particles

This chapter ensures with the addition of alternative methods, the applicability of the test procedures to both biologicals and small molecules. The addition supplements the PDG harmonised text with local requirements (alternative method descriptions) which are marked with white diamonds and which may be used for any type of preparation.

### 3.3.4. Sterile plastic containers for human blood and blood components

Addition of requirements for components of inks, glues and adhesives.

**Tests:** the use of *water for injections R* has been replaced by *water R* (the use of sterilised water for injection is not considered suitable for testing purposes); this change is in accordance with general chapter 3.1.1.1. *Materials based on plasticised poly(vinylchloride) for containers for human blood and blood components*.

**Packaging:** the Section was renamed Storage and the requirements updated.

**Labelling:** the requirement was simplified to keep the reference to relevant national legislation and international agreements only.

### 3.3.8. Sterile single-use plastic syringes

A sentence has been added to clarify that this text is published for information.

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

**Table 5.1.4.-1:** acceptance criteria for the microbiological quality of orodispersible films have been added.

General chapters 2.6.12 and 2.6.13 have been revised to include provisions for addressing the microbiological quality of orodispersible films, published in the same supplement.

This requirement for orodispersible films applies in the Ph. Eur. as a local requirement.

### 5.1.5. Application of the *F* concepts to heat sterilisation processes

The chapter has been revised in order to add a definition of  $F_H$  for dry heat sterilisation and how to calculate it. It is common practice to determine  $F_H$  values for dry heat processes in a similar manner to  $F_0$  for steam sterilisation.

### 5.1.10. Guidelines for using the test for bacterial endotoxins

**Replacement of methods prescribed in monographs (Section 12).** The section has been revised to take into account the new general chapter 2.6.32. *Test for bacterial endotoxins using recombinant factor C*.

For the sake of clarity, the implementation of methods described in the Ph. Eur. and the replacement of methods prescribed in monographs are now described in separate sections (new sections 12 and 13).

### 5.2.2. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs adopted at the 165<sup>th</sup> Commission session.

## GENERAL MONOGRAPHS

### Substances for pharmaceutical use (2034)

**Identification:** to cover the various approaches used in different countries, a sentence has been added to clarify the status of the tests described under the second identification subsection of individual monographs.

## DOSAGE FORMS

### Nasal preparations (0676)

Alignment with the EMA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products.

**Definition:** wording of the different Definition sections modified for greater clarity.

**Production:** instructions for uniformity of delivered dose testing (intra- and inter-container testing) added for metered-dose nasal sprays/powders.

**Labelling:** statements for multi-dose containers added.

**Nasal drops and liquid nasal sprays:** split up into separate subsections.

**Nasal sprays:** uniformity tests updated; Number of deliveries per container and Leak rate tests added.

**Nasal powders:** Uniformity of delivered dose, intra-container testing and Number of deliveries per container tests added for metered-dose nasal powders.

**Semi-solid nasal preparations:** tests section added to cover uniformity tests for single-dose preparations for systemic effect.

### Oromucosal preparations (1807)

Addition of dental preparations, which were included in the different subsections.

Editorial changes introduced to align with similar monographs.

**Gingival solutions:** section integrated into 'Oromucosal solutions, emulsions and suspensions'.

**Oromucosal drops, oromucosal sprays and sublingual sprays:** section divided into 'Oromucosal drops' and 'Oromucosal sprays'.

## VACCINES FOR HUMAN USE

### Diphtheria and tetanus vaccine (adsorbed) (0444)

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452), emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### Diphtheria and tetanus vaccine (adsorbed, reduced antigen(s) content) (0647)

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452) emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### Diphtheria, tetanus and hepatitis B (rDNA) vaccine (adsorbed) (2062)

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452) emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed) (1931)

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452) emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) (2764)

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### **Diphtheria, tetanus and pertussis (whole cell) vaccine (adsorbed) (0445)**

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### **Diphtheria, tetanus and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (2328)**

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The revised monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

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

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### **Diphtheria, tetanus, pertussis (acellular, component) and hepatitis B (rDNA) vaccine (adsorbed) (1933)**

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The revised monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### **Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed) (1934)**

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The revised monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### **Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (2329)**

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The revised monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

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

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The revised monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

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

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The revised monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### **Diphtheria, tetanus, pertussis (whole cell) and poliomyelitis (inactivated) vaccine (adsorbed) (2061)**

**Specific toxicity of the tetanus component:** the requirement to perform the test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The revised monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement, emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

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

**Specific toxicity of the tetanus component:** the requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified tetanus toxoid (cf. monograph on Tetanus vaccine (adsorbed) (0452)). The monograph on Tetanus vaccine (adsorbed) (0452), published in the same supplement,

emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

### **Tetanus vaccine (adsorbed) (0452)**

**Specific toxicity.** The requirement to perform the test for specific toxicity on the product as part of validation of the production process was considered redundant because a more sensitive test for residual toxin is performed routinely on the bulk purified toxoid and the revised monograph emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

**Absence of toxin and irreversibility of toxoid.** The test for irreversibility of the tetanus toxoid is no longer regarded as relevant, in view of data on the stability of the tetanus toxoid and the fact that the tetanus toxin was shown to lose neurotoxic activity under the conditions of the storage test at 37 °C. The test after storage at 5 °C, which was used as a control in the test for irreversibility, has also been removed. The more sensitive test for absence of toxin carried out on non-incubated purified toxoid has been retained.

## VACCINES FOR VETERINARY USE

### **Tetanus vaccine for veterinary use (0697)**

**Preparation of the vaccine (section 2-1) and Residual toxicity (section 3-3).** The requirement to perform the test for residual toxicity on the product as part of validation of the production process was considered redundant because a more sensitive test for residual toxin is performed routinely on the bulk purified toxoid and the revised monograph emphasises the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

A reference to chapter 2.7.27. *Flocculation value (Lf) of diphtheria and tetanus toxins and toxoids* (Ramon assay) has been added.

**Absence of toxin and irreversibility of toxoid (section 2-3-1).** The test for irreversibility of the tetanus toxoid was no longer regarded as relevant, in view of data on the stability of the tetanus toxoid and the fact that the tetanus toxin was shown to lose neurotoxic activity under the conditions of the storage test at 37 °C. The test after storage at 5 °C, which was used as a control in the test for irreversibility, has been removed. The more sensitive test for absence of toxin carried out on non-incubated purified toxoid was retained and fully described to harmonise with the revised monograph for human use *Tetanus vaccine (adsorbed) (0452)* published in the same supplement.



## HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

### Belamcanda chinensis rhizome (2561)

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

**Assay:** reagent used to describe stationary phase modified.

### Caraway fruit (1080)

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

### Clove (0376)

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

### Hawthorn leaf and flower (1432)

**Definition:** 'other European Crataegus species' and Crataegus nigra Waldst. et Kit. no longer mentioned.

**Identification:** macroscopic description updated; illustration of powdered herbal drug introduced and its legend integrated into text; TLC replaced by high-performance thin-layer chromatography (HPTLC) in accordance with chapter 2.8.25.

**Assay:** unspecific absorbance assay replaced by more specific LC assay.

### Hawthorn leaf and flower dry extract (1865)

**Identification:** TLC replaced by high-performance thin-layer chromatography (HPTLC) in accordance with chapter 2.8.25.

**Assay:** unspecific absorbance assay replaced by more specific LC assay.

### Hawthorn leaf and flower liquid extract (1864)

**Identification:** TLC replaced by high-performance thin-layer chromatography (HPTLC) in accordance with chapter 2.8.25.

**Assay:** unspecific absorbance assay replaced by more specific LC assay.

### Lime flower (0957)

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

**Identification C:** TLC replaced by HPTLC in accordance with chapter 2.8.25.

### Lovage root (1233)

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

### Opium dry extract, standardised (1839)

**Assay:** content range for morphine has been widened.

### Passionflower herb (1459)

**Identification:**

- illustration of powdered herbal drug introduced and its legend integrated into text of identification B;

- TLC replaced by high performance thin-layer chromatography (HPTLC) in accordance with chapter 2.8.25.

**Assay:** unspecific photometric assay replaced by LC assay; content limits adapted accordingly.

### Passionflower herb dry extract (1882)

**Identification:** TLC replaced by high performance thin-layer chromatography (HPTLC) in accordance with chapter 2.8.25.

**Assay:** unspecific photometric assay replaced by LC assay; content limits adapted accordingly.

## HOMOEOPATHIC PREPARATIONS

### Homoeopathic preparations (1038)

Homoeopathic dosage form 'liquid preparation for oral use' added:

The use of water in the last potentisation step is allowed.

### Pillules for homoeopathic preparations (2153)

**Uniformity of impregnation.** In addition to method A, using methylene blue, method B, using caffeine as indicator, is added. The test method must be validated to the satisfaction of the competent authority with respect to the size and composition of the pillules, the size of the batch, the equipment, and the procedure used including all relevant variables such as the details of drying and stirring.

## MONOGRAPHS

### Acamprosate calcium (1585)

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

**Impurity A:** reagent used to describe stationary phase modified.

**Related substances:** new test introduced covering 2 new impurities.

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

**Impurities:** section updated.

### Acetylcysteine (0967)

**Content:** lower limit tightened.

**Identification:** description of IR sample preparation deleted; second identification series updated now only describing a mixed melting point test.

**pH:** test deleted.

**Related substances:** method optimised and limits revised.

**Zinc:** use of volumetric solutions avoided and detector wavelength adjusted.

**Assay:** starch solution indicator (which contains mercuric iodide) replaced by potentiometric end-point determination.

**Impurities:** section updated.

### Adrenaline (2303)

**Related substances:** grades of solvents amended in accordance with Technical Guide (2015); use of volumetric solutions avoided; in the preparation of the test solution, mass is expressed using more significant figures due to the quantitative use of this solution; in the preparation of reference solutions (b), (c) and (d), volume is expressed using fewer significant figures due to the qualitative use of these solutions; *adrenaline with impurity F CRS* replaced by *adrenaline impurity F CRS*; reagent used to describe stationary phase modified; Identification of impurities section updated.

**Loss on drying:** subsequent to the revision of general method 2.2.32, the reference to diphosphorus pentoxide has been deleted from this test.

### Ascorbyl palmitate (0807)

**Solution S:** the preparation has been supplemented to specify to dissolve with the aid of ultrasound in order to obtain a clear solution for the tests appearance of solution and specific optical rotation.

### Bambuterol hydrochloride (1293)

**Related substances:** specifications updated to reflect current quality of substances in approved medicinal products on the European market; explicit criterion for unspecified impurities introduced in accordance with the general monograph *Substances for pharmaceutical use (2034)*; grades of solvents amended in accordance with the Technical Guide (2015).

**Impurities:** list updated.

### Betamethasone (0312)

**Identification:** TLC method revised to avoid use of ether; current tests A, D deleted from Second identification.

**Related substances:** in preparation of reference solution (a), volume expressed using fewer significant figures; reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

### Betamethasone acetate (0975)

**Identification:** TLC method revised to avoid use of ether; tests A, E and F deleted from Second identification.

**Related substances:** in preparation of reference solution (a), volume expressed using fewer significant figures; reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

### Betamethasone dipropionate (0809)

**Second identification:** TLC method revised to avoid use of ether; current tests A and E deleted.

**Related substances:** in preparation of reference solutions (a) and (d), volumes expressed using fewer significant figures.

### Bleomycin sulfate (0976)

**Copper:** In line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process. A change to this effect was introduced in the Production section of the general monograph 2034 when revised in Supplement 9.3.

### Borax (0013)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Calcium carbonate (0014)

**Arsenic, Barium:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests have been deleted as the analysis of the batch data shows that these impurities are not present. Therefore, a systematic control is not considered necessary.

### Calcium chloride dihydrate (0015)

**Barium:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Calcium sulfate dihydrate (0982)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Celiprolol hydrochloride (1632)

**Related substances:** specifications updated to reflect quality of substances in approved medicinal products on European market; explicit criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; grades

of solvents amended in accordance with Technical Guide (2015); reagent used to describe stationary phase modified; system suitability criterion amended.

**Impurities:** impurities B to I now listed as unspecified impurities.

### Cetostearyl alcohol (0702)

**Appearance of solution:** preparation of the test solution is clarified.

### Codeine monohydrate (0076)

**Second identification:** UV-spectrophotometry test deleted.

### Codeine phosphate hemihydrate (0074)

**Second identification:** UV-spectrophotometry test deleted.

### Cod-liver oil, farmed (2398)

**Labelling:** section updated to align with monograph *Fish oil, rich in omega-3-acids (1912)*.

### Cyanocobalamin (0547)

**Identification B:** TLC replaced by UHPLC used in test for related substances.

**Related substances:** current method replaced by UHPLC method; individual limits added for impurities.

**Loss on drying:** due to high hygroscopicity of cyanocobalamin, quantity of sample increased to improve accuracy.

**Impurities:** section added.

### Danaparoid sodium (2090)

**Chemical structure:** parent structure corrected and simplified.

**Definition:** limit for potency (anti-factor Xa activity) changed from 11.0-17.0 U/mg to 11.0-19.0 U/mg to reflect currently approved specifications.

**Anti-factor IIa activity:** the anti-factor IIa activity is determined based on the absorbance difference between 2 time points as this has shown improved performance; the temperature at which the test is carried out and storage/handling conditions for the human thrombin solution have been specified; the minimum number of blanks per plate has been corrected to reflect the manufacturer's method.

**Total protein:** it is now stated that the pH of 10.0-10.5 should be obtained at the level of the reaction mixture, in line with what is actually observed; since there is no need for the water content in the bovine albumin used to be limited at maximum 3 per cent (as is the case for *bovine albumin R*) and since this grade of bovine albumin is not easily available on the market, the test now refers to another bovine albumin reagent.

**Assay (anti-factor Xa activity):** the anti-factor Xa activity is determined based on the absorbance difference between 2 time points as this has shown improved performance; the temperature at which the assay is carried out has been specified.

### Deferiprone oral solution (2987)

**Definition:** clarification of scope i.e. restricted to human use.

### Deferiprone tablets (2986)

**Definition:** clarification of scope i.e. restricted to human use.

**Dissolution:** clarification of the path length of the cell.

### Dexamethasone (0388)

**Identification:** TLC method revised to avoid use of ether; current tests A and E deleted from Second identification.

**Related substances:** in preparation of reference solutions (a) and (c), volumes expressed using fewer significant figures; grades of solvents amended in accordance with Technical Guide (2015).

### Dexamethasone acetate (0548)

**Second identification:** TLC method revised to avoid use of ether; current tests A, E and F deleted.

**Related substances:** in preparation of reference solutions (a), (c) and (d), volumes expressed using fewer significant figures; grades of solvents amended in accordance with Technical Guide (2015).

### Dipotassium phosphate (1003)

**Monopotassium phosphate and Assay:** clarification of the calculation, in accordance with the monograph *Disodium phosphate dodecahydrate (0118)*.

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

**Storage:** recommendations have been supplemented.

### Disodium phosphate (1509)

**Monosodium phosphate and Assay:** clarification of the calculation, in accordance with the monograph *Disodium phosphate dodecahydrate (0118)*.

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Disodium phosphate dihydrate (0602)

**Monosodium phosphate and Assay:** clarification of the calculation, in accordance with the monograph *Disodium phosphate dodecahydrate (0118)*.

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Disodium phosphate dodecahydrate (0118)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Epinastine hydrochloride (2411)

**Related substances:** impurity B no longer listed as specified impurity, limit of impurity A decreased, quantitative expression of acceptance criteria introduced; grades of solvents amended in accordance with Technical Guide (2015); reagent used to describe stationary phase modified.

### Epirubicin hydrochloride (1590)

**Definition:** the definition has been revised to clearly indicate that the substance is obtained by semi-synthesis, therefore giving the possibility of producing epirubicin hydrochloride with strains other than *Streptomyces peucetius*.

**Bacterial endotoxins:** test deleted in accordance with Ph. Eur. policy adopted in February 2015 (see Pharmeuropa Online, Technical information).

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

### Ergotamine tartrate (0224)

**Second identification:** UV-spectrophotometry test deleted.

### Etanercept (2895)

**Impurities with molecular masses greater than that of etanercept:** amendment of the system suitability criterion for peak resolution.

**Sialic acid:**

- clarification of the preparation of standard solutions; correction of the concentration range of the standard curve, which was incorrect due to an erroneous introduction an additional pre-dilution step;
- deletion of the sentence 'The following procedure is given as an example', which had been inadvertently introduced, whereas no additional flexibility is needed for this test procedure.

### Everolimus (2918)

The relative retention of impurity E has been corrected.

### Fluoxetine hydrochloride (1104)

**Related substances:** method optimised and limits revised.

**Acetonitrile:** test deleted.

**Sulfated ash:** use of a platinum crucible indicated since the substance contains fluoride.

**Assay:** optimised in line with the proposed new related substances test.

**Impurities:** section updated.

### Human coagulation factor IX (rDNA) concentrated solution (2522)

**Related proteins and impurities:** amendment of the system suitability criterion for the peak-to-valley ratio; the requirement of “minimum 1.5” was lowered to “minimum 1.2”.

### Human coagulation factor IX (rDNA) powder for solution for injection (2994)

**Related proteins:** amendment of the system suitability criterion for the peak-to-valley ratio; the requirement of “minimum 1.5” was lowered to “minimum 1.2”.

### Infliximab concentrated solution (2928)

**Related proteins:** addition of the statement “unless otherwise justified and authorised”, to accommodate for products registered in Europe.

### Isoconazole (1018)

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

**Related substances:** specifications updated to reflect current quality of substances in approved medicinal products on the European market; explicit criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; grades of solvents amended in accordance with Technical guide (2015); system suitability criterion modified.

**Impurities:** transparency list updated.

### Isoconazole nitrate (1017)

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

**Related substances:** specifications updated to reflect current quality of substances in approved medicinal products on the European market; explicit criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; grade of solvents amended in accordance with Technical guide (2015); system suitability criterion modified.

**Impurities:** transparency list updated.

### Ketoconazole (0921)

**Identification:** IR sample preparation deleted.

**Related substances:** specifications updated to reflect the current quality of substances in approved medicinal products on the European market; explicit criterion for unspecified impurities introduced in accordance with the general monograph *Substances for pharmaceutical use (2034)*; system suitability criterion amended.

**Impurities:** section updated.

### Labetalol hydrochloride (0923)

**Related substances:** resolution value and reference solution (b) description amended.

### Lacosamide infusion (2991)

**Definition:** clarification of scope i.e. restricted to human use.



### Lacosamide oral solution (2990)

**Definition:** clarification of scope i.e. restricted to human use.

### Lacosamide tablets (2989)

**Definition:** clarification of scope i.e. restricted to human use.

### Lactose (1061)

**Functionality-related characteristics:** further to the correction of the text by the PDG (October 2019), white diamonds have been added showing that this section is only present in the Ph. Eur. text.

### Lactose monohydrate (0187)

**Microbial contamination:** further to the correction of the text by the PDG (October 2019), the black diamonds have been deleted because the test is harmonised.

**Functionality-related characteristics:** white diamonds have been added showing that this section is only present in the Ph. Eur. text.

### Letrozole (2334)

**Content:** lower limit updated.

**Related substances:** impurity specifications updated to reflect the current quality of approved medicinal products on the European market; reagent used to describe stationary phase modified; grades of solvents amended in accordance with the Technical Guide (2015).

### Magnesium chloride hexahydrate (0402)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Magnesium hydroxide (0039)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Magnesium oxide, heavy (0041)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Magnesium oxide, light (0040)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Magnesium sulfate heptahydrate (0044)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Mexiletine hydrochloride (1029)

**Impurity D:** TLC replaced by LC.

**Related substances:** limits updated to reflect the current quality of substances in approved medicinal products on the European market; reference solution (b) modified following a change in the use of CRS.

### Minocycline hydrochloride dihydrate (1030)

**Related substances:** adjustment of the retention time of minocycline and of the relative retention of impurity E.

### Moxifloxacin hydrochloride (2254)

**Graphic formula, molecular formula and definition:** updated to indicate that the substance may be anhydrous or a hydrate.

**Characters:** statement on hygroscopicity deleted and statement on polymorphism introduced.

**Identification:** recrystallisation step in IR identification added.

**Enantiomeric purity:** system suitability test acceptance criterion widened.

**Related substances:** system suitability test acceptance criterion widened.

### Mupirocin (1450)

**Assay:** a conversion factor for content calculation using *mupirocin lithium CRS* has been introduced.

### Mupirocin calcium (1451)

**Assay:** the conversion factor for content calculation using *mupirocin lithium CRS* has been corrected.

### Mycophenolate sodium (2813)

**Definition:** “semi-synthetic product derived from a fermentation product” statement replaced by “the sodium salt of a fermentation product”.

**Related substances:** new LC method introduced to cover 2 additional impurities; limits modified.

**Assay:** aligned with new method for the test for related substances.

**Impurities:** section updated.

### Ofloxacin (1455)

**Identification B:** reference to optical rotation introduced to differentiate ofloxacin from levofloxacin.

**Absorbance:** non-volumetric solutions now used.

**Impurity A:** TLC test deleted, impurity A now covered by the revised related substances LC test.

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

**Impurities:** section updated.

### **Omega-3-acid triglycerides (1352)**

**Absorbance, Anisidine value, Peroxide value:** limits have been updated based on current products on the European market.

**Partial glycerides:** limits for minimum content of triglycerides and maximum content of ethyl esters and free fatty acids have been introduced. Consequently, the limit for partial glycerides has been deleted.

### **Pentobarbital (0200)**

**Characters:** solubility in heptane added and note on polymorphism introduced.

**Identification:** melting point, TLC and colorimetric tests deleted; IR test introduced.

**Appearance of solution:** reference solution Y<sub>6</sub> replaced by reference solution B<sub>9</sub>.

**Related substances:** limit for total impurities tightened.

### **Pentobarbital sodium (0419)**

**Characters:** solubility in ethanol and heptane added and note on polymorphism introduced.

**Identification:** melting point, TLC and colorimetric tests deleted; IR test added.

**Appearance of solution:** test added.

**Related substances:** limit for total impurities tightened.

### **Potassium chloride (0185)**

**Barium:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### **Potassium clavulanate (1140)**

**Related substances:** indications for identification of impurity G using reference solution (c) were introduced.

### Potassium clavulanate, diluted (1653)

**Related substances:** indications for identification of impurity G using reference solution (c) were introduced.

### Prednisolone acetate (0734)

**Identification:** TLC method revised to avoid use of ether; test D deleted from Second identification.

**Related substances:** in preparation of reference solution (a), volume expressed using fewer significant figures; grades of solvents amended in accordance with Technical Guide (2015).

### Prednisone (0354)

**Second identification:** TLC method revised to avoid use of ether.

**Related substances:** in preparation of reference solutions (a) and (b), volumes expressed using fewer significant figures; grades of solvents amended in accordance with Technical Guide (2015).

### Primidone (0584)

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

**Related substances:** specifications updated to reflect current quality of substances in approved medicinal products on the European market; explicit criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use* (2034).

**Impurities:** transparency list updated.

### Raltegravir chewable tablets (2939)

**Definition:** clarification of scope i.e. restricted to human use.

**Related substances:** in the preparation of reference solution (c), volumes are expressed using fewer significant figures due to the qualitative use of this solution.

### Raltegravir tablets (2938)

**Definition:** clarification of scope i.e. restricted to human use.

**Related substances:** as the maximum daily dose now exceeds 1 g, the reporting threshold has been lowered, in accordance with ICH Q3B.

In the preparation of reference solution (c), volumes are expressed using fewer significant figures due to the qualitative use of this solution.

### Rosuvastatin tablets (3008)

**Definition:** clarification of scope i.e. restricted to human use.

### Salmon oil, farmed (1910)

**Labelling:** section added based on current policy and to align with monograph *Fish oil, rich in omega-3-acids* (1912).

### Silver, colloidal (2281)

The wording “for external use” is deleted from the title of the monograph.

### Sitagliptin tablets (2927)

**Definition:** clarification of scope i.e. restricted to human use.

**Identification A:** range introduced.

**Assay:** conversion factor introduced.

### Sodium acetate trihydrate (0411)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Sodium carbonate (0773)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Sodium carbonate decahydrate (0191)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Sodium carbonate monohydrate (0192)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Sodium dihydrogen phosphate dihydrate (0194)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Sodium hydrogen carbonate (0195)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Sodium laurilsulfate (0098)

This monograph has been revised within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia.

**Identification:** test B deleted and identification by IR introduced as test A; former identification tests A, C et D are maintained as second identification and renamed D, B and C respectively.

**Sodium chloride:** additional instruction included.

**Sodium sulfate:** details regarding the filters have been added.

**Assay:** to improve detection of the end-point, the procedure has been slightly modified.

### Sodium metabisulfite (0849)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Solutions for organ preservation (1264)

Editorial changes introduced to align with similar monographs.

**Definition:** deletion of the reference to 3.3.8, which covers single-use empty syringes and not prefilled syringes.

### Sotalol hydrochloride (2004)

**Related substances:** reagent used to describe stationary phase modified and grades of solvents amended in accordance with Technical Guide (2015).

**Palladium.** In line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted as the relevant elemental impurity is considered to originate from the production process. A change to this effect is introduced in the Production section of the general monograph *Substances for pharmaceutical use (2034)* in Supplement 9.3, as only the manufacturer of a substance for pharmaceutical use knows which elemental impurities may potentially be introduced as catalysts and reagents, and whose levels would therefore need to be controlled.

### Streptomycin sulfate (0053)

**Identification:** introduction of a *streptomycin sulfate for identification CRS* in the TLC identification test.

**Loss on drying:** subsequent to the revision of general method 2.2.32 published in Supplement 9.8, the reference to diphosphorous pentoxide has been deleted from this test.

**Colorimetric test:** test deleted.

**Specific absorbance:** test introduced to replace former colorimetric test.

### Sulfobutylbetadex sodium (2804)

**Assay:** sulfobutylbetadex sodium is a randomly substituted cyclodextrin derivative; hence the peak obtained with the reference solution used for quantitation may not comply with the requirements of general chapter 2.2.46 for symmetry factor (0.8-1.5). A different maximum value has been set.

### Sulfur (0953)

The wording “for external use” is deleted from the title of the monograph.

### Sulfuric acid (1572)

**Arsenic:** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the analysis of the batch data shows that this impurity is not present. Therefore, a systematic control is not considered necessary.

### Tramadol hydrochloride (1681)

**Related substances:** quantitative expression of acceptance criteria introduced; grades of solvents amended in accordance with Technical Guide (2015).

**Assay:** a new titrimetric method giving more reproducible results.

### Tramazoline hydrochloride monohydrate (1597)

**Related substances:** impurity B corrected, impurity C added.

### Vitamin A concentrate (oily form), synthetic (0219)

**Peroxide value.** End point determination potentiometrically.

### Wheat starch (0359)

**Production:** Inclusion of a Production section in view of the EU Guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00 Rev.1) and of the need to monitor the amount of gluten in wheat starch, for patients allergic or intolerant to gluten.

### Wool alcohols (0593)

**Functionality-related characteristics:** section added in analogy to monograph *Wool fat* (0134); cross-reference to melting point and water-absorption capacity test added which are relevant for wool alcohols used in water-emulsifying ointments and lipophilic creams.

### Zinc acexamate (1279)

**Related substances:** reagent used to describe stationary phase modified.

**Arsenic, Cadmium, Lead.** In line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests have been deleted.