Comments concerning revised texts published in Supplement 10.5

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the June 2020 session and published in Supplement 10.5.

When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.5. 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

2.6.27. Microbiological examination of cell-based preparations

Modification of the strain name '*Propionibacterium acnes*' for its new identification '*Cutibacterium acnes*'.

Removal of NCTC 7567 from the *Micrococcus* sp examples as this strain is not a *Micrococcus* sp.

Reordering of the *Clostridium sporogenes* strain examples as ATCC 19404, CIP 79.3 and NCTC 532 are three strains from different collections but identical whereas ATCC 11437 is not identical to them.

2.9.4. Dissolution test for patches

The title and the wording of the chapter have been modified to ensure that it applies to both transdermal and cutaneous patches.

In section 2. Cell method, the calculated volume of the support and the calculated area for the cover of the extraction cell have been corrected.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include new monograph published in Supplement 10.5.

GENERAL MONOGRAPHS

Vaccines for human use (0153)

General provisions. The sentence related to viral safety for vaccines produced using materials of human or animal origin has been revised to clarify that general chapter *2.6.16.*

Tests for extraneous agents in viral vaccines for human use does not apply to egg-derived inactivated influenza vaccines.

The risk of contamination of egg-derived inactivated influenza vaccines by extraneous agents is considered to be minimised, based on the following:

- manufacturers are requested to periodically review their risk assessment and control strategy as regards adventitious agents based on reported emerging adventitious agents;

- influenza virus seeds to be used in vaccine production are propagated in fertilised eggs from chicken flocks that are free from specified pathogens (SPF) in accordance with Ph. Eur. chapter *5.2.2* (requirement of Ph. Eur. monographs on egg-derived inactivated influenza vaccines);

- for production, the virus of each strain is grown in the allantoic cavity of fertilised hens' eggs from healthy flocks (requirement of Ph. Eur. monographs on egg-derived inactivated influenza vaccines);

- there is a species barrier between human viruses and eggs;

- because viral harvests are obtained from eggs from non-SPF flocks and are produced under non-sterile conditions, it is unlikely they would meet the requirements of chapter 2.6.16 for virus harvests;

- the inactivation process must be shown to be capable of inactivating avian leucosis viruses and mycoplasmas (requirement of Ph. Eur. monographs on egg-derived inactivated influenza vaccines);

- the inactivation process must also be validated with respect to a panel of model extraneous agents representative of the potential extraneous agents (requirement in this general monograph for vaccines produced in eggs from healthy, non-SPF flocks);

- viruses potentially present in clinical isolates used to prepare seed lots would be diluted because of the rapid growth of influenza viruses in eggs and/or through the use of gene reassortment techniques.

In addition, the testing strategy and requirements outlined in chapter *2.6.16* may not be fully suitable considering the particularities and constraints related to egg-derived influenza vaccine production.

DOSAGE FORMS

Parenteral preparations (0520)

Definition: wording of the general Definition section of parenteral preparations modified for greater clarity.

Production: statement added that liquid preparations for injection or infusion are practically free from particles; reference to new general chapter *5.17.2* added.

Tests.

- In line with the requirements for liquid parenteral preparations in Europe, compliance with general chapter *2.9.19* is a batch release criterion; unless otherwise justified and authorised, chapter *2.9.19* also applies to suspensions, emulsions and gels for injection.

- In line with the requirements for liquid parenteral preparations in Europe, compliance with general chapter *2.9.20* is a batch release criterion.

- In line with the requirements for parenteral preparations in Europe, compliance with a bacterial endotoxins - pyrogens test is a batch release criterion. The test has been transferred from the individual dosage form subsections to the general Tests section and also updated (e.g. deletion of specified injection volume for pyrogen test, expression of limit for intravitreal preparations).

Injections.

- *Definition:* wording changed to cover radiopharmaceutical preparations and preparations that are further diluted such as glucose solutions; the word 'clear' has been deleted to avoid confusion with opalescence or turbidity.

- *Tests:* uniformity requirements apply to suspensions or emulsions for injection in single-dose containers.

Concentrates for injections or infusions: Labelling section added.

Gels for injection: Tests section added requiring demonstration of appropriate release of active substance(s).

Implants: uniformity tests added.

Intravitreal preparations: subsection added.

Patches (1011)

This monograph applies to both transdermal and cutaneous patches. The title has been adjusted to reflect the change.

Cutaneous patches have been included in this monograph since both transdermal and cutaneous patches have similar manufacturing and quality control requirements.

Preparations for inhalation (0671)

Creation of a section on Preparations for nebulisation, to describe separately Liquid preparations for nebulisation and Powders for liquid preparations for nebulisation.

Semi-solid preparations for cutaneous application (0132)

Latin title: updated.

Medicated plasters and Cutaneous patches: sections transferred to the corresponding dosage form monographs (3032 and 1011, respectively).

Creams, Gels, Pastes: definition updated.

Uniformity requirements: uniformity requirements restructured and changed. For metered-dose preparations intended for systemic effect, inter-container test for uniformity of delivered dose added to Production section and intra-container test to Tests section. Test for uniformity of dosage units for preparations intended for a systemic effect that are supplied in single-

dose containers clarified and possibility of a test for Uniformity of content, where justified and authorised, added.

VACCINES FOR VETERINARY USE

Avian infectious bronchitis vaccine (live) (0442)

Immunogenicity (section 2-3-3). Revised to remove the description of virus recovery from tracheal swabs (section 2-3-3-2) with the aim to encourage manufacturers to develop and use suitably validated alternative methods such as PCR rather than the method using embryonated hens' eggs.

Canine parvovirosis vaccine (live) (0964)

Safety (section 2-3-1): by combining the General safety test (section 2-3-1-1) and the Effects on the thymus test (section 2-3-1-2), the number of dogs to be used has been reduced from 13 to 9 while providing the same safety guarantee.

Equine herpesvirus vaccine (inactivated) (1613)

Batch potency test (section 2-4-2). It has been clarified that preference should be given to in vitro alternative methods for routine testing to encourage their use by manufacturers who have not yet developed them.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Bilberry fruit, dried (1588)

Content: the minimum tannin content was lowered.

Bupleurum root (2562)

Loss on drying: specification widened.

Eucalyptus oil (0390)

Solubility in alcohol: the requirement was adjusted taking the 1,8-cineole content of the oil into account.

Narrow-leaved coneflower root (1821)

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

Assay

- grades of solvents amended in accordance with Technical Guide (2015);

- preparation of test and reference solutions amended to avoid formation of artefact peaks.

Orientvine stem (2450)

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

Pale coneflower root (1822)

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

Assay:

- grades of solvents amended in accordance with Technical Guide (2015);

- preparation of test and reference solutions amended to avoid formation of artefact peaks.

Purple coneflower herb (1823)

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

Assay:

- grades of solvents amended in accordance with Technical Guide (2015);

- preparation of test and reference solutions amended to avoid formation of artefact peaks.

Purple coneflower root (1824)

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

Assay:

- grades of solvents amended in accordance with Technical Guide (2015);

- preparation of test and reference solutions amended to avoid formation of artefact peaks.

HOMOEOPATHIC PREPARATIONS

Anacardium for homoeopathic preparations (2094)

TLC identification of the drug (identification B) and of the mother tincture: HPTLC conditions introduced; gallic acid and caffeic acid reference substances replaced by resorcinol and β-naphthol; UV detection replaced by detection in daylight; TLC chromatograms added in the Knowledge database for information.

Introduction of a section for production of the mother tincture with specific quantities of ethanol.

Magnesium phosphoricum for homoeopathic preparations (2505)

Identification B: improvement of dissolution procedure.

MONOGRAPHS

Alfacalcidol (1286)

Related substances: modification of the preparation of reference solution (c) to ensure enough pre-alfacalcidol is formed; change in the requirements for system suitability to use peaks of impurities A and D for the peak-to-valley ratio determination.

Bacitracin (0465)

Composition: reporting threshold introduced.

Bacitracin zinc (0466)

Composition: reporting threshold introduced.

Betamethasone sodium phosphate (0810)

Identification: TLC revised and current tests A, E and F deleted from the second Identification.

Related substances: grades of solvents amended in accordance with Technical Guide (2015).

Calcium acetate (2128)

Arsenic, Barium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests are deleted.

Calcium stearate (0882)

Cadmium, Lead, Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests are deleted.

Captopril (1079)

Loss on drying: the wording has been aligned with conditions described in the general chapter *2.2.32*.

Castor oil, refined (2367)

Composition of fatty acids: clarification of limits. A chromatogram for information is added.

Castor oil, virgin (0051)

Composition of fatty acids: clarification of limits. A chromatogram for information is added.

Ciclosporin (0994)

Definition: wording adjusted to clearly indicate fermentation as the only means by which the substance is obtained.

Related substances, Assay: chromatographic conditions adjusted and impurity limits adapted based on batch data.

Loss on drying: vacuum pressure increased to reflect the equipment performances.

Impurities: specified and other detectable impurities distinguished; impurity F introduced and ciclosporins (different from ciclosporin A) listed individually.

Clomifene citrate (0997)

Related substances: impurities B, D, G and H are now specified.

Clotrimazole (0757)

Related substances: grades of solvents amended in accordance with Technical Guide (2015); reference solution (b) diluted and resolution requirement adjusted accordingly; reagent used to describe stationary phase modified; identification of impurities section added; second system suitability test requirement deleted.

Codeine phosphate sesquihydrate (0075)

Second identification: UV-spectrophotometry test deleted as not practicable in pharmacies.

Related substances: test replaced by UHPLC method covering additional impurities.

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

Copper sulfate (0893)

Lead: in line with the Ph. Eur. Implementation strategy for the ICH Q3D guideline on elemental impurities the test will be kept with the updated limit.

Dacarbazine (1691)

Identification: use of volumetric solutions avoided in test A.

Related substances: new reference solutions added to allow a better determination of impurity contents; reagent used to describe stationary phase modified; identification of impurities sections included; retention time of dacarbazine and relative retention of impurity B updated in test B; relative retention of citric acid and the need to disregard its peak in the estimation of total impurities, added in test B.

Impurity D: alternative GC method introduced.

Dexamethasone sodium phosphate (0549)

Second Identification: TLC revised, current tests A, E and F deleted.

Related substances and Assay: grade of solvents amended in accordance with Technical Guide (2015).

Dihydrostreptomycin sulfate for veterinary use (0485)

Definition: following the implementation of the HPLC method, the lower content limit of 95.0 % for the sum of dihydrostreptomycin sulfate and streptomycin sulfate was deemed to be too restrictive for products previously approved with the microbiological assay. Consequently, the lower limit of 95.0 % was adjusted to 94.0 %.

Related substances: introduction of the newly established *Streptomycin sulfate for identification CRS*.

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

Erythropoietin concentrated solution (1316)

Definition: the term 'average glycosylation pattern' was removed.

Production: Glycan analysis test consisting of an outline of the method to be followed and a detailed example procedure resulting from the project of the Biological Standardisation Programme of EDQM (BSP144) was introduced, significantly improving the quality of the monograph while maintaining its flexibility; The requirement for consistency of production with respect to glycosylation pattern was also introduced.

Identification: N-terminal sequence analysis (Identification E) was judged as no longer relevant as a release test and was therefore deleted.

Dimers and related substances with molecular masses greater than that of erythropoietin: the column diameter was changed to reflect current availability and practice.

Ferrous fumarate (0902)

Arsenic, Chromium, Lead, Nickel: in line with the Ph. Eur. Implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limits for Arsenic, Lead and Nickel and with the current limit for Chromium. In addition, the following impurities will be added: Cobalt (20 ppm) and Vanadium (40 ppm).

Cadmium, Mercury: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests are deleted.

Ferrous gluconate hydrate (0493)

Title: supplemented according to current policy on hydrates (see PA/PH/SG (15) 68 DEC).

Arsenic: in line with the Ph. Eur. Implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the current limit. In addition, the following impurities will be added: Cobalt (25 ppm), Nickel (50 ppm) and Vanadium (50 ppm).

Barium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Fludarabine phosphate (1781)

Related substances: CRS strategy modified with a view to no longer using *fludarabine phosphate CRS* for peak identification purposes. New reference solution for peak identification containing *fludarabine for peak identification CRS* (containing impurity C).

Gemcitabine hydrochloride (2306)

Related substances: impurity C quantified using the corresponding CRS. Acceptance criteria expressed in quantitative mode.

Bacterial endotoxins: test deleted.

Gliclazide (1524)

Related substances: particle size of stationary phase updated; grade of acetonitrile and water in mobile phase amended in accordance with Technical Guide (2015).

Impurity B: retention time of impurity B updated.

Glipizide (0906)

Second identification revised: UV spectrophotometry and TLC replaced by a mixed melting point.

Heparin calcium (0332)

Identification E: reference to the general chapter *2.3.1* replaced with cross-reference to quantitative test for calcium already present in the Test section.

Heparins, low-molecular-mass (0828)

Identification C: number of theoretical plates deleted from the column description.

Identification D: reference to the general chapter *2.3.1* replaced with cross-reference to quantitative tests for sodium or calcium (as appropriate) already present in the Test section.

Assay: clarification about possible use of automated methods and hence adjustment of volumes introduced; *reagent tris(hydroxymethyl)aminomethane sodium chloride buffer solution pH 7.4 R* modified to allow the use of Macrogol 6000, preferred stabiliser in automated system due to reduced foaming.

Kanamycin acid sulfate (0033)

Identification A: introduction of the newly established *Streptomycin sulfate for identification CRS*.

Kanamycin monosulfate (0032)

Identification A: introduction of the newly established *Streptomycin sulfate for identification CRS*.

Assay: corresponding CRS to be used mentioned in addition to the reference to general chapter *2.7.2*.

Lamivudine (2217)

Related substances: in the preparation of reference solution (b), the mass is expressed using more significant figures, in the preparation of reference solutions (d) and (e), the volumes are expressed using fewer significant figures, reagent used to describe stationary phase modified.

Enantiomeric purity: description of the stationary phase updated to ensure that only columns that allow to meet the system suitability requirements are used.

Magnesium carbonate, heavy (0043)

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Omeprazole (0942)

Loss on drying: the wording has been aligned with conditions described in the general chapter *2.2.32*.

Paroxetine hydrochloride hemihydrate (2018)

Related substances: description of reference solution (b) modified according to the change in production of *paroxetine for system suitability CRS*.

Penicillamine (0566)

Impurity A: CRS strategy modified with a view to no longer using *penicillamine CRS* for peak identification purposes. New reference solution for system suitability described, containing the substance to be examined and *penicillamine disulfide CRS* (impurity A).

Loss on drying: normal vacuum is appropriate.

Phosphoric acid, concentrated (0004)

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

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

Phosphoric acid, dilute (0005)

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

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

Ramipril (1368)

Loss on drying: the wording has been aligned with conditions described in the general chapter *2.2.32*.

Ranitidine hydrochloride (0946)

Loss on drying: the wording has been aligned with conditions described in the general chapter *2.2.32*.

Sodium bromide (0190)

Identification B: it is considered sufficient to use only reaction (a).

Somatostatin (0949)

Related substances: limits for specified and unspecified impurities introduced in line with current batch data; limit for specified impurities B and F expressed to reflect that they originate from different processes but elute at the same retention time; reagent used to describe stationary phase modified; grades of solvents amended in accordance with Technical Guide (2015).

Impurities: section added.

Sulindac (0864)

Identification: 2nd identification series deleted.

Related substances: impurity specifications updated; explicit criterion for unspecified impurities introduced in line with general monograph *Substances for pharmaceutical use (2034)*; ethanol-free chloroform in the mobile phase replaced by methylene chloride.

Titanium dioxide (0150)

Antimony, Arsenic, Barium: in line with the Ph. Eur. Implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limits. In addition, the following impurity will be added: Lead (5 ppm).

Zidovudine (1059)

Related substances: impurity specifications updated; system suitability criterion amended accordingly.

Zinc stearate (0306)

Cadmium, Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests are deleted.