Comments concerning texts published in Supplement 11.7

Brief descriptions of the modifications that have been made to new, revised and corrected texts adopted by the European Pharmacopoeia Commission at the June session and published in Supplement 11.7 are provided below. Please note that these descriptions are not provided systematically for new and corrected texts, but are instead provided on a case-by-case basis. This information is reproduced in the Knowledge database under View history.

All revised, corrected or deleted parts of a text published in the online version of the European Pharmacopoeia are now indicated by change marks in the form of triangles. For reasons of readability, these triangles are not shown in the print version, but users will still be able to determine if a text has been corrected or revised from the version date indicated above the title of the monograph and, if applicable, by 'corrected X.X', indicating publication of a corrected version in Supplement X.X.

GENERAL CHAPTERS

5.2.12. Raw materials of biological origin for the production of cell-based and gene therapy medicinal products

The revision is the consequence of the publication in the same Ph. Eur. Supplement of the new general monograph *Gene therapy medicinal products for human use (3186)*, which replaces general chapter *Gene transfer medicinal products for human use (5.14)*:

Preamble: deletion of the sentence 'this chapter is published for information' because general monograph *3186* refers to general chapter *5.2.12* on raw materials and therefore, as stated in the General Notices, chapter *5.2.12* becomes mandatory when referred to in general monograph *3186*.

Vectors: replacement of the reference to general chapter *5.14*, following its suppression, with a reference to the new general monograph *3186*.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs.

5.34. Additional information on gene therapy medicinal products for human use

This general chapter provides recommendations in addition to the requirements of the general monograph *Gene therapy medicinal products for human use (3186)* and comprises individual sections covering gene therapy medicinal products (GTMPs) that have not yet been approved on the European market.

The general requirements for GTMP production, for recombinant vectors and for genetically modified cells for human use are outlined in a dedicated section in the general monograph *3186*. The statements therein, including the flexibility of performing the tests listed under respective headings at an alternative stage of the process under a suitable testing scheme in justified cases, are not repeated in the individual sections of the general monograph or this general chapter.

This general chapter contains four sections that constitute revised versions of the corresponding ones in general chapter *5.14*: Plasmid vectors for human use, Adenovirus vectors for human use, Poxvirus vectors for human use and Retroviridae-derived vectors for human use. The requirements for bacterial cells used for the production of plasmid vectors - outlined in a dedicated section in general chapter *5.14* - are now included in the section on plasmid vectors for human use. Finally, the general chapter contains the completely new section Genetically modified bacterial cells for human use.

It is emphasised that plasmid vectors for human use describe plasmid vectors for direct administration to humans and not for preparation of other recombinant vectors that may be subsequently administered to humans or used for cell modification. Several individual sections within this general chapter and general monograph *3186* contain requirements for plasmids used in the production of a given recombinant vector.

The possibility of testing for bacterial endotoxins using recombinant factor C (rFC) as described in general chapter *2.6.32* as well as the classic limulus amoebocyte lysate (LAL)-based methods for the quantification of endotoxins from gram-negative bacteria has been introduced in the general chapter.

The Genetically modified bacterial cells section requests a suitable test for pyrogenicity. The addition of a reference to a new general chapter on Pyrogenicity (*5.1.13*), which is currently being elaborated and will provide guidance for the selection and implementation of such a test, is envisaged when the chapter in question is published in the Ph. Eur.

Additional information can be also found in a separate explanatory document in the Knowledge Database.

GENERAL MONOGRAPHS

Gene therapy medicinal products for human use (3186)

This general monograph provides a framework of requirements for the production and control of gene therapy medicinal products (GTMPs) and is partially reproduced from general chapter *5.14. Gene transfer medicinal products for human use*, which was elaborated when no such products had yet been approved on the European market.

The text is designed to be applicable to approved products. The need for partial or complete application of the requirements to products used during the different phases of clinical trials is decided by the competent authority.

The general monograph defines GTMPs in accordance with the Directive 2009/120/EC.

It contains a section outlining general requirements for GTMP production, for recombinant vectors and for genetically modified cells for human use. This section has been substantially expanded from the original section in general chapter *5.14* and provides common requirements for these classes of products. These requirements are applicable to all GTMPs within the defined scope and are not necessarily repeated in individual sections.

In addition to a General requirements section containing provisions on the production of all GTMPs and specific requirements for recombinant vectors and genetically modified cells for human use, the general monograph contains three individual sections describing additional requirements for genetically modified human autologous cells, adeno-associated virus

vectors for human use and recombinant oncolytic herpes simplex viruses for human use, reflecting the products currently approved on the European market. The section Adeno-associated virus vectors for human use constitutes the revised version of the corresponding one in general chapter *5.14*, while the two remaining sections were newly drafted.

Due to the specific nature of GTMPs, this general monograph refers to the risk-based approach according to Directive 2001/83/EC, which may be applied in order to meet the quality requirements defined herein.

The possibility of testing for bacterial endotoxins using recombinant factor C (rFC) as described in general chapter *2.6.32* as well as the classic limulus amoebocyte lysate (LAL)-based methods for the quantification of endotoxins from gram-negative bacteria has been introduced in the monograph.

In addition to this general monograph, an accompanying general chapter Additional information on gene therapy medicinal products for human use (*5.34*) containing supplementary recommendations on GTMPs not yet on the European market is also provided to assist users.

Consequently, the general monograph *Gene therapy medicinal products for human use (3186)* and the general chapter Additional information on gene therapy medicinal products for human use (*5.34*) replace the general chapter *Gene transfer medicinal products for human use* (*5.14*), which is now obsolete. Additional information can be also found in a separate explanatory document in the Knowledge Database.

Recombinant DNA technology, products of (0784)

It has been clarified in the preamble that this monograph is also applicable to vaccine antigens for veterinary use produced by rDNA technology.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Gallium (^{68}Ga) chloride (accelerator-produced) solution for radiolabelling (3109)

Identification D: The test using the cationic exchange column has been deleted. The four remaining identification tests together are sufficient to confirm the identity of the preparation.

Technetium (^{99m}Tc) oxidronate injection (2376)

Definition: the substance is now defined as a complex derived from sodium [^{99m}Tc] pertechnetate and sodium oxidronate in the presence of a reducing agent. Information related to the quality of sodium pertechnetate (^{99m}Tc) has been transferred to the newly created Production section.

Production: section created requiring that *Sodium pertechnetate (^{99m}Tc) injection (fission) (0124)*, *Sodium per-technetate (^{99m}Tc) injection (non-fission) (0283)* or *Sodium pertechnetate (^{99m}Tc) injection (accelerator-produced) (2981*) are used to prepare Technetium (^{99m}Tc) oxidronate injection.

Radiochemical purity, impurity A: use of a reagent that cross-refers to the monographs of *Sodium pertechnetate (^{99m}Tc) injection (fission) (0124)*, *Sodium pertechnetate (^{99m}Tc) injection (non-fission) (0283)* and *Sodium pertechnetate (^{99m}Tc) injection (accelerator-produced) (2981)*.

Radiochemical purity, impurity B: replacement of TLC test by paper chromatography test, as this replacement represents an analytical improvement.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Hop strobile (1222)

Characters: deleted as odour not highly characteristic and cannot be described with reference to the odour of a single compound.

Foreign matter: taking into account batch data received and the harvesting techniques used, separate limits for foreign organs and foreign elements have been introduced.

Platycodon root (2660)

Identification B (English version only): text clarified and aligned with the French version.

Identification C: description of the solid phase extraction (SPE) cartridge detailed.

Quillaia bark (1843)

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

MONOGRAPHS

Amiodarone hydrochloride (0803)

Identification B: test modified in order to avoid the use of potassium dichromate (REACH).

Related substances: new LC procedure which is able to separate all impurities; limits revised based on recent batch data.

Iodides: concentrations of hydrochloric acid and potassium iodate converted from molarity to g/L.

Loss on drying: change to standard vacuum conditions.

Aprotinin concentrated solution (0579)

Related substances. The limit of maximum 2.3 per cent for all impurities eluted after the principal peak was introduced based on current batch data. The retention time of the peak due to aprotinin was amended.

Baclofen (0653)

Content: lower limit increased in line with Technical Guide.

Second identification: UV procedure deleted as TLC procedure considered sufficient for the purpose of the second identification. In the TLC (identification B), chloroform replaced by methylene chloride in the mobile phase; detection in ultraviolet light at 254 nm introduced and reagent '*TLC silica gel G plate R*' replaced by '*TLC silica gel F_{254} plate R*'.

Identification A (IR): preparation of the KBr discs deleted.

Related substances: LC procedure completely revised to cover additional impurities; impurity limits updated according to recent batch data.

Brivaracetam (3139)

Stereoisomeric purity: introduction of a signal-to-noise ratio to ensure the sensitivity of the procedure.

Calcium ascorbate dihydrate (1182)

Related substances: based on feedback from users and on additional experimental verification, amount of potassium dihydrogen phosphate in solution A increased from 17 g/L to 68 g/L to ensure full precipitation of calcium and to avoid system over-pressure and shut down.

Carmellose sodium, low-substituted (1186)

Settling volume: the level of precision of the volume has been adjusted to the use of a 100 mL graduated cylinder.

identification B: colour description changed from "reddish-purple" to "reddish-violet" because of varying national interpretations of the colour purple. This purely editorial change is in accordance with the Ph. Eur. Style Guide and has no impact on the conditions or requirements of the test.

Cefamandole nafate (1402)

Related substances: the reagent used to describe the stationary phase has been modified.

Sodium carbonate: due to rapid hydrolysis, the sodium carbonate (Na_2CO_3) originally present in cefamandole nafate is immediately converted to sodium bicarbonate ($NaHCO_3$) when the substance is placed in aqueous solution. Therefore, only one equivalent of hydrochloric acid (HCl) is needed to titrate the Na_2CO_3 in the test solution and to reach the end-point. Consequently, the equivalence between the volume of HCl and the quantity of Na_2CO_3 has been revised.

Ciclopirox olamine (1302)

Related substances: reagent used to describe stationary phase modified.

Cinnarizine (0816)

Acidity or alkalinity: test deleted as the test for related substances (specific chromatographic method with high sensitivity) is considered sufficient.

Related substances: impurities B and D specified in order to reflect the quality of substances in approved medicinal products on the European market; system suitability criterion amended to avoid the use of an external compound.

Loss on drying: conditions of drying clarified and aligned with the French version.

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

Impurities: section updated.

Dexamfetamine sulfate (2752)

Enantiomeric purity: system suitability test acceptance criterion widened based on recent experimental results, replacing the SST acceptance criterion for resolution by a minimum peak-to-valley ratio.

Dextromethorphan hydrobromide monohydrate (0020)

Related substances: quantitative style now prescribed and use of a diluted solution of the test solution at 0.1 per cent prescribed for the impurity quantitation; correction factor for impurity C deleted; impurity limits updated to reflect current quality of the products on the market: impurities A, B, C and D listed as unspecified impurities and limit for total impurities tightened from 1.0 per cent to 0.5 per cent.

Doxylamine hydrogen succinate (1589)

Characters: the information that the substance is hygroscopic has been added.

Storage: taking into account the need to protect the substance from light and based on work confirming the hygroscopicity of this substance, an appropriate section has been introduced to guide users on suitable storage.

Dronedarone hydrochloride tablets (3038)

Title: in accordance with the policy decided by the Ph. Eur. Commission regarding the titles of monographs on medicinal products containing chemically defined active substances presented as a salt, “hydrochloride” added to the monograph title.

Erythritol (1803)

Related substances. Column particle size of stationary phase corrected.

Fludrocortisone acetate (0767)

Content: Limits updated to reflect the liquid chromatography (LC) assay.

Identification: Thin-layer chromatography in first identification series replaced by LC assay.

Specific optical rotation: Dioxan replaced by less toxic solvent; limits adjusted accordingly.

Related substances: More robust method introduced to allow the separation of additional impurities; impurity specifications updated to reflect the quality of substances in approved medicinal products on the European market.

Assay: Absorbance test replaced by LC for related substances.

Storage: taking into account data from approved manufacturers, an appropriate section has been introduced to guide users on suitable storage.

Impurities: Transparency list introduced.

Hydroxypropylcellulose, low-substituted (2083)

Settling volume: the level of precision of the volume has been adjusted to the use of a 100 mL graduated cylinder.

Naloxone hydrochloride dihydrate (0729)

Appearance of solution: limit for the colour of solution updated.

Related substances: new impurity H introduced as unspecified impurity; grade of acetonitrile and tetrahydrofuran amended in accordance with the Technical Guide; reagent used to describe stationary phase modified.

Impurities: impurity H added.

Phenylalanine (0782)

Specific optical rotation: if necessary, sonication can be used to dissolve the substance.

Rosuvastatin calcium tablets (3008)

Title: in accordance with the policy decided by the Ph. Eur. Commission regarding the titles of monographs on medicinal products containing chemically defined active substances presented as a salt, “calcium” added to the monograph title.

Sitagliptin phosphate tablets (2927)

Title: in accordance with the policy decided by the Ph. Eur. Commission regarding the titles of monographs on medicinal products containing chemically defined active substances presented as a salt, “phosphate” added to the monograph title.

Sorafenib tosilate tablets (3022)

Title: in accordance with the policy decided by the Ph. Eur. Commission regarding the titles of monographs on medicinal products containing chemically defined active substances presented as a salt, “tosilate” added to the monograph title.

Sorbitol, liquid, partially dehydrated (2048)

Assay: following the improvements made to the chromatographic conditions (published in Supplement 11.5), the resolution criterion has been tightened in line with the values obtained.