Comments concerning texts published in Supplement 11.8

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 11.8 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

2.4.20. Determination of elemental impurities

This text corresponds to the sign-off text signed by the Pharmacopoeial Discussion Group (PDG). The coordinating pharmacopoeia is the United States Pharmacopoeia. Non-harmonised attributes are placed between black diamonds (♦♦), while local requirements only present in the Ph. Eur. text are placed between white diamonds (◊◊). A footnote has been included in the text referring to the general chapter *5.8. Pharmacopoeial harmonisation* to indicate that the text has now been harmonised through the PDG.

Compared to the general chapter published in the 11th Edition of the Ph. Eur., the text underwent a complete revision. However the general approach for the determination of elemental impurities is mostly preserved. In this context it is emphasised that procedures 1 and 2 are provided as examples. The user is free to use any analytical procedure provided it satisfies the corresponding validation requirements detailed in the general chapter.

2.5.44. Capillary isoelectric focusing for recombinant therapeutic monoclonal antibodies

This general chapter describes in detail the execution of two capillary isoelectric focusing (cIEF) procedures - one based on conventional systems (Procedure A) and one on imaged systems (Procedure B) - as well as considerations on system performance, system suitability, assay acceptance criteria, data analysis and evaluation of results. The two sets of test conditions described in this general chapter may be used as is or can be considered as starting conditions for the development of a cIEF or imaged cIEF procedure for a specific monoclonal antibody (mAb). The extent of optimisation of the analytical procedure should be determined based on suitability for an individual mAb (case-by-case). General recommendations on aspects to consider for product-specific application, including analytical procedure development and validation, are also given.

The general chapter is the result of experimental work undertaken by a number of laboratories to verify the applicability of these two procedures as suitable multi-product procedures for analysing charge heterogeneity of mAbs. Results of this study are discussed in the publication

Ascione A *et al*. Charge heterogeneity of therapeutic monoclonal antibodies by different cIEF systems: views on the current situation. mAbs 2024;16(1). doi:10.1080/19420862.2024.2313737.

2.6.30. Monocyte-activation test

Guidance notes, 2-5. Cross-validation: considerations regarding the risk assessment to support the use of the test for bacterial endotoxins as the sole method to assess pyrogenicity, previously described in general chapter *5.1.10. Guidelines for using the test for bacterial endotoxins*, is now described in general chapter *5.1.13. Pyrogenicity*. To reflect this situation, the reference to general chapter *5.1.10* has been replaced by a reference to general chapter *5.1.13*.

2.6.40. Monocyte-activation test for vaccines containing inherently pyrogenic components

Introduction: considerations regarding the risk assessment to support the use of the test for bacterial endotoxins as the sole method to assess pyrogenicity, previously described in general chapter *5.1.10. Guidelines for using the test for bacterial endotoxins*, is now described in general chapter *5.1.13. Pyrogenicity*. To reflect this situation, the reference to general chapter *5.1.10* has been replaced by a reference to general chapter *5.1.13*.

2.7.24. Flow cytometry

This general chapter is submitted without change marks to improve readability as editorial changes have been made throughout the text.

The main modifications to the chapter are:

- *structure:*
  - *the introduction has been separated into a preamble and a 'Principles' section;*
  - *a new 'Technical considerations' section groups together the equipment description (flow cell, light sources, signal detection, signal management and analogue-to-digital conversion) and system selection;*
  - *a new 'Sample preparation' section has been added;*
  - *'Data acquisition and analysis' is now an independent section;*
  - *new sections have been added to the end of the chapter: 'Application', Qualification' and 'Validation';*
- *a reference to general chapter 5.1.6. Alternative methods for control of microbiological quality has been added when flow cytometry procedures are used for the control of microbiological quality;*
- *the analysis of small particles (e.g. exosomes and viral particles) has been included;*
- *the 'Signal detection' subsection now contains a table describing fluorescent dyes and probes commonly used in flow cytometry, adapted from McKinnon KM. Flow Cytometry: An Overview. Current Protocols in Immunology 2018;120(1):5.1.1-5.1.11. DOI: 10.1002/cpim.40;*
- *a stepwise procedure to establish compensation has been added as an example;*
- *a subsection has been added to help users select a flow cytometry system;*

– *the new 'Sample preparation' section gives examples of processing steps and staining procedures;*

– *the gating strategy notion has been introduced in the 'Data acquisition and analysis' section;*

– *the 'System suitability criteria' subsection (formerly the 'Internal control' section) has been developed in order to give more guidance;*

– *examples of flow cytometry application are given in a new section;*

– *guidance on qualification and validation has been included in the respective sections.*

3.1.3. Polyolefins

Production: the chemical name of plastic additive 10 has been changed in the English version to align it with the wording used in other texts on plastic materials. No change has been made to the equivalent section in the French version as the chemical name was already aligned.

Appearance: general chapter *3.1* covers "Materials used for the manufacture of containers". Therefore, only characteristics specific to the material have been kept while those related to containers have been omitted.

Identification C: a temperature range at which the material is expected to melt has been added to avoid unintended decomposition.

Reducing substances: the volumes of solution S1 and *0.002 M potassium permanganate* have been expressed using more significant figures to ensure appropriate precision of the titration.

3.1.4. Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations

Appearance: general chapter *3.1* covers "Materials used for the manufacture of containers". Therefore, only characteristics specific to the material have been kept while those related to containers have been omitted.

Reducing substances: the volumes of solution S1 and *0.002 M potassium permanganate* have been expressed using more significant figures to ensure appropriate precision of the titration.

3.1.5. Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations

Production: the chemical name of plastic additive 10 has been changed in the English version to align it with the wording used in other texts on plastic materials. No change has been made to the equivalent section in the French version as the chemical name was already aligned.

Appearance: general chapter *3.1* covers "Materials used for the manufacture of containers". Therefore, only characteristics specific to the material have been kept while those related to containers have been omitted.

Identification C: a temperature range at which the material is expected to melt has been added to avoid unintended decomposition.

Reducing substances: the volumes of solution S1 and *0.002 M potassium permanganate* have been expressed using more significant figures to ensure appropriate precision of the titration.

3.1.6. Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations

Appearance: general chapter *3.1* covers “Materials used for the manufacture of containers”. Therefore, only characteristics specific to the material have been kept while those related to containers have been omitted.

Identification C: a temperature range at which the material is expected to melt has been added to avoid unintended decomposition.

Reducing substances: the volumes of solution S1 and *0.002 M potassium permanganat*e have been expressed using more significant figures to ensure appropriate precision of the titration.

3.1.7. Poly(ethylene - vinyl acetate) for containers and tubing for total parenteral nutrition preparations

Appearance: general chapter *3.1* covers “Materials used for the manufacture of containers”. Therefore, only characteristics specific to the material have been kept while those related to containers have been omitted.

Reducing substances: the volumes of solution S1 and *0.002 M potassium permanganate* have been expressed using more significant figures to ensure appropriate precision of the titration.

3.3.4. Sterile plastic containers for human blood and blood components

Pyrogens: the requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has therefore been deleted.

The limit for pyrogenicity is expressed by the requirement “as approved by the competent authority”.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this general chapter does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their containers and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

3.3.7. Sets for the transfusion of blood and blood components

Pyrogens: the requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has therefore been deleted.

The limit for pyrogenicity is expressed by the requirement “as approved by the competent authority”.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this general chapter does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their sets and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

5.1.10. Guidelines for using the test for bacterial endotoxins

The revision of this general chapter is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") from the Ph. Eur.

General chapter *5.1.10* has been revised further to the publication of general chapter *5.1.13. Pyrogenicity* as certain parts of *5.1.10* (first paragraph of section 1 Introduction, section 3 Risk assessment, and section 12 Implementation of methods described in the Ph. Eur.) have been moved to *5.1.13*.

In addition, other parts of chapter *5.1.10* have been deleted as they were considered to be either no longer applicable or redundant after the publication of *5.1.13*. Section 13 Replacement of a method prescribed in a monograph has been deleted as the notion, already described in the General Notices, is the subject of general chapter *5.27. Comparability of alternative analytical procedures*. References to the rabbit pyrogen test have also been removed.

A reference to general chapter *2.6.32. Test for bacterial endotoxins using recombinant factor C* has been included in the introduction, as the guidance provided in this chapter may also apply.

5.1.13. Pyrogenicity

This general chapter provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test).

It contains certain parts taken from general chapter *5.1.10. Guidelines for using the text for bacterial endotoxins*, in particular the considerations on the risk assessment and on the implementation of methods.

The elaboration of general chapter *5.1.13* is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur. The detailed strategy of the Ph. Eur. Commission for removing the rabbit pyrogen test is described in a document published on Pharmeuropa online (https://go.edqm.eu/NewPyrogenicityStrategy).

Importantly this general chapter does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

5.2.6. Evaluation of safety of veterinary vaccines and immunosera

This general chapter has been modified together with the general monograph *"Vaccines for veterinary use"* (*0062*) and chapter *5.2.7. "Evaluation of efficacy of veterinary vaccines and immunosera"* to clarify that other forms of vaccines such as recombinant or nucleic acid-based (DNA or RNA) vaccines are in the scope of the Ph. Eur.

Note that “DNA vaccines” are defined in the general monograph *0062* in section 1-4 as nucleic acid-based vaccines containing DNA encoding one or more antigen(s).

3 ECOTOXICITY. For DNA vaccines, a greater level of investigation due to the greater potential impact and consequences of use of vector vaccines in the environment (compared to a conventional vaccine) is requested, in particular the potential risk of migration of the DNA to gonadal tissues and potential DNA transfer into germ line cells of vaccinated male and female animals and thus potential transmission to offspring must be considered.

5.2.7. Evaluation of efficacy of veterinary vaccines and immunosera

This general chapter has been modified together with the general monograph *“Vaccines for veterinary use”* (*0062*) and chapter *5.2.6. “Evaluation of safety of veterinary vaccines and immunosera*” to clarify that other forms of vaccines such as recombinant or nucleic acid-based vaccines (DNA or RNA) vaccines are in the scope of the Ph. Eur.

Note that “vector vaccines” are defined in the general monograph *0062* in section 1-3.

In addition, although these other vaccine forms are not covered by the Definition section of individual monographs, it has been clarified that the immunogenicity test described in these monographs (when available and applicable) nevertheless applies. It is also specified which individual monograph is then to be followed (live or inactivated), depending on the different situations: how the immune system is stimulated, the type of insert, if the vector is replication-competent, etc.

5.2.11. Carrier proteins for the production of conjugated polysaccharide vaccines for human use

Pyrogenicity: the requirement for Bacterial endotoxins has been replaced with a new requirement for Pyrogenicity, referring to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test).

The new pyrogenicity requirement applies to all carrier proteins. As a result, the test for pyrogens in rabbits (“rabbit pyrogen test”) described for OMP has been deleted.

It should be noted that the revision of this general chapter is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this general chapter does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 1 new monograph.

5.31. Phage therapy medicinal products

Pyrogenicity. The text has been aligned with that of other Ph. Eur. monographs and general chapters containing a requirement on pyrogenicity. In particular, a reference to general chapter *5.1.13. Pyrogenicity*, which provides guidance for the selection and implementation of a suitable test for pyrogenicity, has been introduced.

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

Pyrogenicity. The text has been aligned with that of other Ph. Eur. monographs and general chapters containing a requirement on pyrogenicity. In particular, a reference to general chapter *5.1.13. Pyrogenicity*, which provides guidance for the selection and implementation of a suitable test for pyrogenicity, has been introduced.

GENERAL MONOGRAPHS

Immunosera for human use, animal (0084)

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test).

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Pharmaceutical preparations (2619)

Tests: Pyrrolizidine alkaloids (PAs) are nitrogen-containing compounds that occur naturally in plants. Several hundred structurally distinct PAs have been found in several thousand different plant species. Many of these plants are common weeds, which can contaminate raw plant materials used for the production of medicinal products. This results in contamination by PAs of raw plant materials but also other natural products such as honey, usually at very low levels. A reference to the general chapter *Contaminant pyrrolizidine alkaloids* (*2.8.26*) has been added to make the useful guidance provided therein more visible to users.

Radiopharmaceutical preparations (0125)

Bacterial endotoxins - Pyrogens. This requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The references to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), have therefore been deleted. In addition, the rabbit pyrogen test has been replaced by the monocyte-activation test as a test that may be prescribed when the nature of the radiopharmaceutical preparation results in interference in the test for bacterial endotoxins and it is not possible to eliminate the interfering factors.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Substances for pharmaceutical use (2034)

Bacterial endotoxins and Pyrogens. The requirements for Bacterial endotoxins and for Pyrogens have been replaced with a single new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted from this general monograph.

This revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

In accordance with this revision, a substance for pharmaceutical use complies with the test for bacterial endotoxins described in general chapters *2.6.14* or *2.6.32* if it is labelled as endotoxin-free grade, or with a suitable test for pyrogenicity if it is labelled as pyrogen-free grade.

Importantly, the revision of this general monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Vaccines for human use (0153)

The requirement for Bacterial endotoxins in the Tests section of this general monograph has been replaced with a new requirement on Pyrogenicity, referring to general chapter *5.1.13. Pyrogenicity* which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The new requirement in the Tests section (test on the final vaccine) applies to vaccines intended for parenteral administration.

In addition, a statement has been introduced under General provisions in the Production section of the monograph to stress the need to characterise pyrogenicity during development studies and to consider the impact of subsequent manufacturing changes on pyrogenicity.

This revision of general monograph *0153* is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this general monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Vaccines for veterinary use (0062)

This general monograph has been modified together with both general chapters *5.2.6 "Evaluation of safety of veterinary vaccines and immunosera"* and *5.2.7 "Evaluation of efficacy of veterinary vaccines and immunosera"* to clarify that other forms of vaccines such as recombinant or nucleic acid-based (DNA or RNA) vaccines are in the scope of the Ph. Eur.

The definition section has been amended and a section 1- 4 “DNA and RNA vaccines” has been added. In the production section, amendments have also been made to cover recombinant or nucleic acid-based vaccines (for ex. addition of genetic and phenotypic characterisation), in particular under section 2-4 “Manufacturer’s tests,” where the formulation of the vaccine is based on the nucleic acid content instead of the antigen content, where appropriate (see new section 2-4-2).

In addition, the following modifications have been made:

– *in the introductory note, the reference to the EMA/CVMP Guideline has been deleted to be in line with the requirements in Annex II of the new veterinary Regulation (EU) 2019/6, which has replaced “minor use” by “limited market”, and which is no longer in the scope of this guideline. Nevertheless, “minor use” has still to be considered in some countries that have ratified the European Pharmacopoeia Convention (ETS No. 050) - which is much wider than the European Union - therefore the reference to the EMA/CVMP Guideline has been deleted but the sentence kept.*

– *Bacterial vaccines (section 1-1): the exemption for vaccines prepared in cell cultures or in live animals has been deleted and therefore this section applies to such vaccines too (if any). Bacterial toxoids are already covered by bacterial vaccines, therefore they have been deleted in the title of section 1-1 (but this is only editorial as they are still in the scope).*

– *Stability (section 2-2-3). To align with the current legislations (new vet. legislation and VICH) and to current practice, the request to use consecutive batches has been removed (as they have to be representative).*

– *Bacterial vaccines (section 2-3-2-3-1) : to include all possible substrates used for the production of bacterial vaccines, “production medium” has been replaced by “substrate for production”.*

DOSAGE FORMS

Intravesical preparations (2811)

Bacterial endotoxins - Pyrogens: this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal from the Ph. Eur. of the rabbit pyrogen test.

Importantly, the revision of this general monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their preparations and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Orodispersible films (3195)

This new monograph covers preparations that are applied in the mouth where they disintegrate rapidly before being swallowed. The active substance is mainly absorbed from the gastrointestinal tract. As these are not oromucosal preparations, it was considered necessary to elaborate a separate monograph.

In the monograph *Oromucosal preparations (1807)*, it is proposed to change the name of the "Orodispersible films" subsection to "Oromucosal films" in order clearly to indicate that, in that case and in contrast to this newly proposed monograph, the absorption of the active substance occurs mainly through the oral mucosa.

Oromucosal preparations (1807)

Introduction of a new section on sublingual lyophilisates to differentiate from oral lyophilisates.

Labelling section updated to include instructions for multidose preparations.

Oromucosal drops:

– *definition revised to indicate that the preparations are administered in small volumes as drops by means of a suitable device such as a dropper; this change has been introduced in order clearly to distinguish oromucosal drops from oromucosal solutions;*

– *tests for uniformity of dosage units (2.9.40), uniformity of content and uniformity of mass of oromucosal drops supplied in single dose containers have been deleted from the Tests section since it is already listed in the general Tests section;*

– *test for uniformity and accuracy of dose added to ensure consistency in requirements for oral and oromucosal drops.*

Oromucosal sprays:

– *intra- and inter-container testing requirements for the uniformity of delivered dose added in the Production section to ensure consistency with requirements for other spray dosage forms (e.g. nasal sprays) ;*

– *test for uniformity of delivered dose (or mass, if applicable) added to include a uniformity requirement for preparations supplied in multidose containers;*

– *tests for uniformity of dosage units (2.9.40) and for uniformity of mass removed from the Tests section for oromucosal sprays since they are already included in the general Test section;*

– *test for number of deliveries per container added in the Tests section to ensure consistency with requirements for other spray dosage forms (e.g. ear sprays, nasal sprays).*

Orodispersible films section renamed Oromucosal films to reflect the intended site of administration and absorption of this type of film and to differentiate them from the orodispersible films, which are intended to be swallowed after dispersion in the mouth.

Parenteral preparations (0520)

Bacterial endotoxins - pyrogens: this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins

or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted.

This revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

In accordance with this revision, a parenteral preparation complies with the test for bacterial endotoxins described in general chapter *2.6.14* or *2.6.32* if it is labelled as free from bacterial endotoxins, or with the monocyte-activation test described in general chapter *2.6.30* if it is labelled as apyrogenic.

Importantly, the revision of this general monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their parenteral preparations and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Preparations for irrigation (1116)

Pyrogens and Bacterial endotoxins: the requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted from this general monograph. Consequently, in order to avoid redundancies, the requirement for Bacterial endotoxins has also been removed, as general chapter *2.6.14* is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their preparations and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

VACCINES FOR HUMAN USE

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

General provisions: the requirement to validate the manufacturing process to demonstrate that the product, if tested, would comply with the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens*, has been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

Bacterial endotoxins (Tests section): the requirement for Bacterial endotoxins, including the requirement to carry out the rabbit pyrogen test if any components of the vaccine prevent the determination of endotoxin, has been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply. In the Tests section, the introductory sentence has also been updated as a result of the deletion of the test for bacterial endotoxins.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

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

General provisions: the requirement to carry out a pyrogen test in rabbits during development studies and wherever revalidation is necessary and the reference to general chapter *2.6.8. Pyrogens* have been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

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

General provisions: the requirement to validate the manufacturing process to demonstrate that the product, if tested, would comply with the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens*, has been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

Bacterial endotoxins (Tests section): the requirement for Bacterial endotoxins, including the requirement to carry out the rabbit pyrogen test if any components of the vaccine prevent the determination of endotoxin, has been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply. In the Tests section, the introductory sentence has also been updated as a result of the deletion of the test for bacterial endotoxins.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the

pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Haemophilus type b and meningococcal group C conjugate vaccine (2622)

General provision: the requirement to carry out a pyrogen test in rabbits during development studies and wherever revalidation is necessary and the reference to general chapter *2.6.8. Pyrogens* have been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Haemophilus type b conjugate vaccine (1219)

General provisions. The requirement to validate the manufacturing process to demonstrate that the product, if tested, would comply with the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens*, has been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

Bacterial endotoxins (Tests section). The requirements for Bacterial endotoxins, including the requirement to carry out the rabbit pyrogen test if any components of the vaccine prevent the determination of endotoxin, has been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Hepatitis B vaccine (rDNA) (1056)

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Meningococcal group A, C, W135 and Y conjugate vaccine (3066)

General provisions: the requirement to validate the manufacturing process to demonstrate that the product, if tested, would comply with the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens*, has been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Meningococcal group C conjugate vaccine (2112)

General provisions: the requirement to carry out a pyrogen test in rabbits during development studies and wherever revalidation is necessary and the reference to general chapter *2.6.8. Pyrogens* have been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Meningococcal polysaccharide vaccine (0250)

Pyrogens (under Purified polysaccharides): the requirement for Pyrogens, referring to general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test).

Pyrogens (under Tests): the requirement for Pyrogens, including a reference to general chapter *2.6.8. Pyrogens*, has been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Pneumococcal polysaccharide conjugate vaccine (adsorbed) (2150)

General provisions. The requirement to carry out a pyrogen test in rabbits during development studies and wherever revalidation is necessary, including a reference to general chapter *2.6.8. Pyrogens*, has been deleted. As a result, the requirement to characterise pyrogenicity during development laid down in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, applies.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Pneumococcal polysaccharide vaccine (0966)

Pyrogens. The requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Rabies vaccine for human use prepared in cell cultures (0216)

Bacterial endotoxins, Pyrogens: the requirements for Bacterial endotoxins and for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), have been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Tick-borne encephalitis vaccine (inactivated) (1375)

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been deleted. As a result, the requirements for pyrogenicity in the revised general monograph *Vaccines for human use (0153)*, published in the same Supplement, apply. Under Final lot, a sentence has also been updated as a result of the deletion of the pyrogen test.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

VACCINES FOR VETERINARY USE

Salmonella Enteritidis vaccine (live, oral) for chickens (2520)

Immunogenicity (2-2-2): it has been clarified that all the samples collected from vaccinates and controls during the observation period at the given time points have to be taken into account to show the significant reduction compared to the controls.

Salmonella Typhimurium vaccine (live, oral) for chickens (2521)

Immunogenicity (2-2-2): it has been clarified that all the samples collected from vaccinates and controls during the observation period at the given time points have to be taken into account to show the significant reduction compared to the controls.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Gallium (^{68}Ga) chloride (generator-produced) solution for radiolabelling (2464)

TITLE and PRODUCTION: Both sections now reflect that the solution is prepared using a generator. This allows it to be distinguished from a gallium (^{68}Ga) solution prepared by an accelerator which has a different impurity profile and is subject of the monograph *gallium (^{68}Ga) chloride (accelerator-produced) solution for radiolabelling (3109)*.

DEFINITION: It is indicated that gallium is present as a trichloride.

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.

Sterility: A test has been included in case of use of the solution in e.g. radiopharmaceutical kits, in which no further sterilisation process is performed before administration to the patient.

Bacterial endotoxins: Bacterial endotoxins are now limited per batch produced, instead of per maximum volume of a patient dose. This modification takes account of the fact that generator-produced gallium (^{68}Ga) chloride for radiolabelling is not directly for patient use but used for the preparation of injectable radiopharmaceutical preparations.

Labelling: As a consequence of expressing the bacterial endotoxin limit per batch produced, the indication of the maximum volume used for the preparation of a single patient dose on the label of the preparation is no longer needed and thus deleted.

Technetium (^{99m}Tc) human albumin injection (0640)

Definition: the information related to the quality of sodium pertechnetate (^{99m}Tc) and human albumin has been transferred from the Definition section to the newly created Production section. The redundant statement that the human albumin solution is apyrogenic has been deleted. The information related to the ratio of tin to albumin and the limit for tin have been deleted from the Definition as in the Tests section the amount of tin is anyway limited to 1 mg per millilitre.

Production: section created to clarify that either *Sodium pertechnetate (^{99m}Tc) injection (fission) (0124)* or *Sodium pertechnetate (^{99m}Tc) injection (non-fission) (0283)* or *Sodium pertechnetate (^{99m}Tc) injection (accelerator-produced) (2891)* is to be used in combination with *Human albumin solution (0255)* for the preparation of technetium (^{99m}Tc) human albumin injection.

Tetra-*O*-acetyl-mannose triflate for radiopharmaceutical preparations (2294)

Characters: the statement on hygroscopicity has been deleted as the substance is not hygroscopic.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Ash leaf (1600)

Definition: term ‘hydroxycinnamic acid derivatives’ replaced by ‘*ortho*-diphenolic compounds’ to accurately describe the content in this herbal drug.

Assay: term ‘hydroxycinnamic acid derivatives’ replaced by ‘*ortho*-diphenolic compounds’ to accurately describe the content in this herbal drug.

Black horehound (1858)

Definition: term ‘*ortho*-hydroxycinnamic acid derivatives’ replaced by ‘*ortho*-diphenolic compounds’ to accurately describe the content in this herbal drug.

Assay: term ‘*ortho*-hydroxycinnamic acid derivatives’ replaced by ‘*ortho*-diphenolic compounds’ to accurately describe the content in this herbal drug.

Burdock root (2943)

Definition: term ‘hydroxycinnamic acid derivatives’ replaced by ‘*ortho*-diphenolic compounds’ to accurately describe the content in this herbal drug.

Assay: term ‘hydroxycinnamic acid derivatives’ replaced by ‘*ortho*-diphenolic compounds’ to accurately describe the content in this herbal drug.

Horse-chestnut bark (2945)

Assay: procedure optimised by using mobile phase A as diluent in order to reduce the noise observed around the retention time of the peak due to esculin.

Moutan bark (2474)

Definition: content limits relaxed based on recent batch data.

Narrow-leaved coneflower root (1821)

Identification: test C by TLC (*2.2.27*) and test D by LC (*2.2.29*) deleted and replaced by new tests C and D, both by HPTLC in line with general chapter *2.8.25*; these new tests have been harmonised with other revised Echinacea monographs (*1822*, *1823* and *1824*) and new test D (as described in the test for "Other Echinacea species") allows users to distinguish the herbal drug from other Echinacea species.

Echinacea purpurea: replaced by a test for other Echinacea species by HPTLC in line with general chapter *2.8.25*.

Pale coneflower root (1822)

Identification: test C by TLC (*2.2.27*) and test D by LC (*2.2.29*) deleted and replaced by new tests C and D, both by HPTLC in line with general chapter *2.8.25*; these new tests have been harmonised with other revised Echinacea monographs (*1821*, *1823* and *1824*) and new test D (as described in the new test for "Other Echinacea species") allows users to distinguish the herbal drug from other Echinacea species.

Other Echinacea species and Parthenium integrifolium: replaced by a test for other Echinacea species by HPTLC in line with general chapter *2.8.25*; the test for Parthenium integrifolium is covered by this new procedure and identification test C.

Pumpkin seed (2941)

Identification: test B optimised to improve the microscopic identification of hull-less varieties of *Cucurbita pepo* L.

Purple coneflower herb (1823)

Identification: test C by TLC (*2.2.27*) and test D by LC (*2.2.29*) deleted and replaced by new tests C and D, both by HPTLC in line with general chapter *2.8.25*; these new tests have been harmonised with other revised Echinacea monographs (*1821*, *1822* and *1824*) and new test D (as described in the new test for "Other Echinacea species") allows users to distinguish the herbal drug from other Echinacea species.

Other Echinacea species: new HPTLC procedure added.

Purple coneflower root (1824)

Identification: test C by TLC (*2.2.27*) and test D by LC (*2.2.29*) deleted and replaced by new tests C and D, both by HPTLC in line with general chapter *2.8.25*; these new tests have been harmonised with other revised Echinacea monographs (*1821*, *1822* and *1823*) and new test D (as described in the new test for "Other Echinacea species") allows users to distinguish the herbal drug from other Echinacea species.

Other Echinacea species and Parthenium integrifolium: replaced by a test for other Echinacea species by HPTLC in line with general chapter *2.8.25*; the test for Parthenium integrifolium is covered by this new procedure and identification test C.

Ribwort plantain (1884)

Definition: term '*ortho*-dihydroxycinnamic acid derivatives' replaced by '*ortho*-diphenolic compounds' to accurately describe the content in this herbal drug.

Assay: term '*ortho*-dihydroxycinnamic acid derivatives' replaced by '*ortho*-diphenolic compounds' to accurately describe the content in this herbal drug.

Rosemary leaf (1560)

Definition: botanical name updated.

Content: expressed as "*ortho*-diphenolic compounds" instead of "hydroxycinnamic derivatives" as the described determination method is based on Arnow's reaction, which determines not solely hydroxycinnamic derivatives but *ortho*-diphenolic compounds in general.

Identification: as essential oils are already determined in the assay, tests C and D (thin-layer chromatography on essential oils and on flavonoids and phenolic acids, respectively) have been replaced by a new test C describing a high-performance thin-layer chromatography procedure on flavonoids and phenolic acids in accordance with general chapter *2.8.25*.

Assay of essential oils: as the best results were obtained when the assay was performed without using an organic solvent when collecting the distillate in the graduated tube, this has been specified.

HOMOEOPATHIC PREPARATIONS

Cuprum aceticum for homoeopathic preparations (2146)

Identification A: identification of acetates by odour (reaction (a)) has been replaced by a more suitable method (infrared absorption spectrophotometry).

Nickel: in line with the Ph. Eur. strategy for implementation of the ICH Q3D guideline on elemental impurities (switch to ICH Q3D requirements), the test is proposed for deletion. It should be noted that these tests are no longer included in individual monographs published in the European Pharmacopoeia (please see press release published on 11 January 2017).

MONOGRAPHS

Amikacin sulfate (1290)

Pyrogens. The requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test"), has been deleted. As a

result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Assay. Following assessment, the existing symmetry factor requirement has been deleted from the monograph so that the default symmetry factor requirement (0.8-1.8) of the revised general chapter *2.2.46*. (Ph. Eur. 11th Edition) applies.

Anticoagulant and preservative solutions for human blood (0209)

Pyrogens. The requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is based on 5 IU of endotoxin per kilogram rabbit body mass as the pyrogenic dose, taking into account the injection volume.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Anti-T lymphocyte immunoglobulin for human use, animal (1928)

Pyrogens (2.6.8): this requirement has been replaced with a requirement on Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted.

The limit for pyrogenicity is expressed by the requirement “as authorised by the competent authority”.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Bovine serum (2262)

Haemoglobin: tightening the limit of 4 mg/mL to 0.5 mg/mL to better reflect batch contents.

Calcium levulinate dihydrate (1296)

Identification C: use of 2,4 dinitrophenylhydrazine should be avoided due to lack of availability and because it is explosive. The test is proposed for deletion since remaining tests are considered sufficient (SIT Working Party recommendation).

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Chloramphenicol sodium succinate (0709)

Related substances: the grade of solvents has been amended in accordance with the Technical Guide for the elaboration of monographs.

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Chlorhexidine digluconate solution (0658)

Related substances: the analytical procedure has been optimised to allow better control of the impurities; impurity Q has now been identified; the system suitability criteria have been updated in view of the modified procedure.

Impurities: a structure is now proposed for impurity Q.

Colistimethate sodium (0319)

Related substances: the system suitability requirement for the retention times has been revised.

Pyrogens. The requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been deleted. As a

result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

3-*O*-Desacyl-4′-monophosphoryl lipid A (2537)

Pyrogens: the test for pyrogens in rabbits (“rabbit pyrogen test”), conducted on the trimethylamine salt of 3-*O*-desacyl-4’-monophosphoryl lipid A, has been replaced by the monocyte-activation test.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Dicloxacillin sodium monohydrate (0663)

Title: the degree of hydration has been added.

Related substances: the grade of solvents has been amended in accordance with the Technical Guide.

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Doxapram hydrochloride monohydrate (1201)

Title: revised to add degree of hydration in accordance with Ph. Eur. policy.

Content: range updated based on the recommendations of the Technical Guide and batch data.

Related substances: column dimensions modified to improve the peak symmetry and flow rate decreased accordingly; grades of solvents amended in accordance with the Technical Guide; in the preparation of reference solution (b), volume/mass expressed using fewer significant figures due to the qualitative use of this solution; concentration of the solution used for quantitation lowered from 0.2 per cent to 0.1 per cent; quantitative style now prescribed; introduction of a limit at 0.10 per cent for unspecified impurities; impurity limits updated to reflect current quality of the products on the market: impurities A and B listed as unspecified impurities and limit for total impurities tightened from 1.0 per cent to 0.5 per cent.

Assay: preparation of the solution modified to avoid solubility issues.

Flucloxacillin sodium monohydrate (0668)

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test"), has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Impurities: as the structure of impurity J is unknown, the previously proposed structure has been deleted.

Flumetasone pivalate (1327)

Identification: TLC from the 1st series replaced by a cross-reference to LC assay.

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

Assay: UV absorbance assay replaced by LC for related substances.

Glucose (0177)

Pyrogens. The requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted.

The new limit for pyrogenicity is expressed in endotoxin equivalents per milligram and is based on 5 IU of endotoxin per kilogram rabbit body mass as the pyrogenic dose, taking into account the injection volume. Where the test for bacterial endotoxins is selected, this limit will be expressed in IU of endotoxin per milligram.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment on pyrogenicity.

Glucose monohydrate (0178)

Pyrogens. The requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The

reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted.

The new limit for pyrogenicity is expressed in endotoxin equivalents per milligram and is based on 5 IU of endotoxin per kilogram rabbit body mass as the pyrogenic dose, taking into account the injection volume. Where the test for bacterial endotoxins is selected, this limit will be expressed in IU of endotoxin per milligram.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment on pyrogenicity.

Haemodialysis, solutions for (0128)

Bacterial endotoxins (2.6.14), Pyrogens (2.6.8). The requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity,* published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has been deleted. Consequently, in order to avoid redundancies, the requirement for Bacterial endotoxins (*2.6.14*) has also been removed, as general chapter *2.6.14* is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their preparations and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Haemofiltration and haemodiafiltration, solutions for (0861)

Bacterial endotoxins (2.6.14), Pyrogens (2.6.8). The requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has been deleted. Consequently, in order to avoid redundancies, the requirement for Bacterial endotoxins (*2.6.14*) has also been removed, as general chapter *2.6.14* is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their preparations and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human albumin solution (0255)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted from this text. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limits for pyrogenicity are expressed in endotoxin equivalents per millilitre and are obtained from the previous limits in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, these limits are still expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human antithrombin III concentrate (0878)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement on Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of antithrombin III and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of antithrombin III.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human C1-esterase inhibitor (2818)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of human C1-esterase inhibitor and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of human C1-esterase inhibitor.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human coagulation factor VII (1224)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxin*s has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicit*y.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of human coagulation factor VII and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of human coagulation factor VII.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human coagulation factor VIII (0275)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted. The reference

general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of factor VIII:C and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of factor VIII:C.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human coagulation factor IX (1223)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted from this text. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of human coagulation factor IX and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of human coagulation factor IX.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human coagulation factor XI (1644)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted. Consequently, in order to avoid redundancies, the reference to the test for bacterial endotoxins described in general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the as general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of human coagulation factor XI and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of human coagulation factor XI.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human fibrinogen (0024)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted from this text. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity.*

The limit for pyrogenicity is expressed in endotoxin equivalents per milligram of fibrinogen and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per milligram of fibrinogen.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human normal immunoglobulin for intramuscular administration (0338)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human normal immunoglobulin for intravenous administration (0918)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14). This requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limits for pyrogenicity are expressed in endotoxin equivalents per millilitre and are obtained from the previous limits in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, these limits will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human normal immunoglobulin for subcutaneous administration (2788)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human plasma (pooled and treated for virus inactivation) (1646)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has been deleted. The reference to general

chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human α-1-proteinase inhibitor (2387)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per milligram of human α-1-proteinase inhibitor and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per milligram of human α-1-proteinase inhibitor.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human prothrombin complex (0554)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14). This requirement has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of human coagulation factor IX and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of human coagulation factor IX.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Human von Willebrand factor (2298)

Pyrogens (2.6.8) or Bacterial endotoxins (2.6.14): this requirement has been replaced with a new requirement for Pyrogenicity. This new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”) has therefore been deleted. The reference to general chapter *2.6.14. Bacterial endotoxins* has also been deleted, as the general chapter is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per IU of human von Willebrand factor and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per IU of human von Willebrand factor.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Kanamycin acid sulfate (0033)

Identification: test B, using the reaction of the substance with picric acid, has been deleted to avoid the use of this explosive and toxic reagent.

Loss on drying: the vacuum pressure has been adjusted to reflect the equipment performances. The sample size has been adjusted to 1.000 g in accordance with the Technical Guide.

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* (“rabbit pyrogen test”), has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Editorial changes have also been made throughout the monograph.

Kanamycin monosulfate monohydrate (0032)

Title: the degree of hydration has been added.

Identification: test B, using the reaction of the substance with picric acid, has been deleted to avoid the use of this explosive and toxic reagent.

Loss on drying: the vacuum pressure has been adjusted to reflect the equipment performances.

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test"), has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Methylene chloride (0932)

Definition: amended to fit with the wording and limits in the test for Ethanol, 2-methylbut-2-ene and volatile impurities.

Ethanol, 2-methylbut-2-ene and volatile impurities: the symmetry factor for the peak due to ethanol is constantly lower than the default requirement of chapter *2.2.46* (0.8-1.8). A specific requirement (minimum 0.6) is therefore included in the monograph.

Water: sample size expressed with a lesser accuracy in accordance with the Technical Guide (three significant figures).

Peritoneal dialysis, solutions for (0862)

Bacterial endotoxins (2.6.14), Pyrogens (2.6.8). The requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has been deleted. Consequently, in order to avoid redundancies, the requirement for Bacterial endotoxins (*2.6.14*) has also been removed, as general chapter *2.6.14* is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the

pyrogenicity of their preparations and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Polymyxin B sulfate (0203)

Pyrogens: the requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test"), has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Composition: in the preparation of reference solutions (a) and (b), volumes expressed using more significant figures due to the quantitative use of the solutions (S/N ratio).

Procainamide hydrochloride (0567)

Related substances: the procedure based on thin-layer chromatography has been replaced by a liquid chromatography procedure. The list of impurities and their specifications have been revised accordingly: three impurities are now listed as unspecified impurities.

Other changes (e.g. Definition, Characters, Identification and Tests) are editorial.

Propylthiouracil (0525)

Related substances: impurity B limit widened from 0.10 per cent to 0.2 per cent based on batch data.

Simeticone (1470)

Phenylated compounds: introduction of an optional centrifugation step in case the test solution is not clear due to non-soluble components.

Sodium citrate dihydrate (0412)

Title: hydration form identified in the title according to current policy on hydrates.

Pyrogens. The requirement for Pyrogens, including a reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test"), has been deleted. As a result, the new requirements for pyrogenicity in the revised general monograph *Substances for pharmaceutical use (2034)*, published in the same Supplement, apply.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their products and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Sodium molybdate dihydrate (1565)

Definition: the upper limit for content has been increased to 102.0 per cent based on batch data and in accordance with the Technical Guide recommendation for complexometric titrations.

Solutions for organ preservation (1264)

Pyrogens and Bacterial endotoxins: the requirement for Pyrogens has been replaced with a new requirement for Pyrogenicity. The new requirement refers to general chapter *5.1.13. Pyrogenicity*, published in the same Supplement, which provides guidance for the selection and implementation of a suitable test for pyrogenicity (test for bacterial endotoxins or monocyte-activation test). The reference to the pyrogen test in rabbits described in general chapter *2.6.8. Pyrogens* ("rabbit pyrogen test") has therefore been deleted from this monograph. Consequently, in order to avoid redundancies, the requirement for Bacterial endotoxins has also been removed, as general chapter *2.6.14* is now referred to in general chapter *5.1.13. Pyrogenicity*.

The limit for pyrogenicity is expressed in endotoxin equivalents per millilitre and is obtained from the previous limit in the test for bacterial endotoxins. Where the test for bacterial endotoxins is selected, this limit will still be expressed in IU of endotoxin per millilitre.

It should be noted that this revision is part of a broader exercise affecting multiple Ph. Eur. texts and aiming at the complete removal of the rabbit pyrogen test from the Ph. Eur.

Importantly, the revision of this monograph does not call into question strategies involving the test for bacterial endotoxins that are already used by manufacturers to control the pyrogenicity of their preparations and have been authorised by the competent authority, nor is it intended to prompt a retrospective assessment of pyrogenicity.

Sorafenib tosilate (2931)

Related substances: following approval of a marketing authorisation for a new source, test revised to cover two additional specified impurities (I and J) and increase the limit for impurity E, which becomes a specified impurity. The limits introduced are those approved for this new source based on ICH Q3A (maximum 1.0 mg daily intake of impurities for a daily dose of 800 mg of sorafenib tosilate); resolution criterion lowered to "minimum 1.5" since several manufacturers could not comply with "minimum 2.5" - the high column temperature could be the reason for the resolution worsening as the number of injections increases.

Thiamazole (1706)

Definition: lower content limit tightened based on available batch data.

Identification: upper limit of test A (melting point) widened to 147 °C according to batch data; editorial changes made in test B; description of sample preparation in test C deleted, thus not restricting the measurement mode to transmission.

Solution S: deleted as only used in one test.

Related substances: method optimised to improve sensitivity and replace the use of chloroform; limits tightened based on available batch data; addition of a limit for unspecified impurities; acceptance criteria expressed in quantitative style.

Assay: amount of water reduced to achieve a better fit with current equipment.

Impurities: section updated in accordance with the limits in the test for related substances

Zinc acetate dihydrate (1482)

Identification A: reaction (b) of general chapter *2.3.1* amended with adjustment of pH to slightly alkaline and filtration, as these additional steps are necessary for the identification of acetates of this substance.

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