Comments concerning texts published in Issue 13.1

Brief descriptions of the modifications that have been made to new, revised and corrected texts adopted by the European Pharmacopoeia Commission at the November session and published in Issue 13.1 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 European Pharmacopoeia are indicated by change marks in the form of triangles.

GENERAL CHAPTERS

2.1.7. Balances for analytical purposes

Definitions of multi-interval and multiple range balances introduced. Clarifications of technical terms relating to equipment performance made. Section on minimum weight expanded.

2.4.35. Extractable elements in plastic materials for pharmaceutical use

Determination: a non-exhaustive list of elements determined using this analytical procedure has been included to enhance the clarity of the text.

2.5.43. Size exclusion chromatography for recombinant therapeutic monoclonal antibodies

This new general chapter describes two size exclusion chromatography (SEC) procedures – HPLC (Procedure A) and UHPLC (Procedure B) – as suitable generic procedures for determination of the monomer and high molecular weight species in monoclonal antibodies (mAbs) in order to monitor their stability, quality and production consistency.

It provides a detailed description of the execution of these two procedures, as well as considerations on system performance, system suitability, sample acceptance criteria, data analysis and results evaluation. 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 (U)HPLC procedure for a specific 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 practical aspects related to sample preparation and use of control samples, as well as on points to consider for the validation approach required for a specific mAb (including an overview of analytical procedure performance), are also given.

This general chapter is the result of experimental work undertaken by a number of laboratories to verify the applicability of these two procedures. The suitability of these procedures in terms of accuracy, precision and linearity over the reportable range has been demonstrated during validation experiments using a set of mAbs.

2.6.14. Bacterial endotoxins

This general chapter has been revised to introduce the fluorimetric end-point method using recombinant factor C (rFC) as the new method G. The proposed technical content concerning method G in the Introduction and sections 2 and 9 has been imported from general chapter *2.6.32. Test for bacterial endotoxins using recombinant factor C*. Some editorial adjustments have also been made to the Introduction and sections 5 and 6 to take account of the new method.

General chapter *2.6.32* became obsolete as a result of the introduction of rFC in this general chapter and has therefore been suppressed. In addition, general chapter *5.1.13. Pyrogenicity* has been revised in the same issue of the European Pharmacopoeia, to take account of these considerations.

The changes to this PDG harmonised general chapter have been introduced as local Ph. Eur. requirements, i.e. as an additional method in the Ph. Eur. It is therefore placed between white diamonds.

2.6.39. Microbiological examination of human tissues

Final control testing: the reference to general chapter *2.6.32* has been deleted following the inclusion of its contents as method G in general chapter *2.6.14* and its subsequent suppression from the Ph. Eur. (Issue 13.1); the reference to bacterial endotoxins (*2.6.14*, *2.6.30*) has been replaced by a reference to pyrogenicity (*5.1.13*) since general chapter *5.1.13* applies to both endotoxin and non-endotoxin pyrogen testing and provides guidance to users on the choice of test.

2.8.25. High-performance thin-layer chromatography of herbal products

Title: the text now refers more generally to “herbal products”, giving the possibility to apply the HPTLC technique beyond herbal drugs and herbal drug preparations.

Equipment: greater details are given on suitable equipment for performing HPTLC analysis.

Preparation of solutions: additional information is given on the preparation of reference solutions used for establishing the minimum content of selected markers, and for limit tests for adulterants.

Preparation of the chromatographic system: as an alternative, application of reference solutions containing more than one substance may now be carried out through the successive application (also known as co-spotting) of individual solutions of the prescribed concentration.

Saturation of the chamber: a description of how to saturate chambers is included.

Development of the plate: a description of how the development in an unsaturated chamber is performed is included.

System suitability test: the basis for developing system suitability tests is not restricted to the separation of only two substances that migrate closely but that are narrowly separable under the specified chromatographic conditions. Individual monographs may prescribe the use of *HPTLC system suitability solution CRS* as the reference solution for carrying out the system suitability test. This CRS is a solution of eight different organic compounds dissolved in methanol. It allows the verification of the adequate performance of the chromatographic system for the entire R_F range of a HPTLC plate, by yielding an even distribution over the whole R_F range of at least three of the eight constituents for a large variety of developing

solvents covering a wide range of polarities and selectivities on silica gel 60 F_{254}. The evaluation is done at 254 nm without derivatisation, and the corresponding acceptance criteria are based on the position in the chromatogram of the zones due to some, or all, of the eight constituents, although it is possible that not all eight constituents will be separated.

Visual evaluation: additional information is given on carrying out the visual evaluation of HPTLC plates for the evaluation of minimum content of prescribed markers(s), and for limit tests for adulterants.

Quantitative evaluation: a new section on quantitative evaluation has been introduced, hence extending the scope of this general chapter to the use of HPTLC in quantitative analysis. The use of thin-layer chromatography for quantitative analysis is already covered in general chapter *2.2.27.*

2.9.1. Disintegration of tablets and capsules

This text corresponds to the sign-off text signed by the Pharmacopoeial Discussion Group (PDG) in June 2025.

Compared to the general chapter published in the 11th Edition of the Ph. Eur., the following changes are included:

– Test B (intended for tablets and capsules larger than 18 mm) has been harmonised, including the introduction of an additional requirement for the inner diameter of the beaker;

– the dimensional requirements for the basket-rack assembly are now given in a consistent manner across tests A and B;

– the general chapter now explicitly allows the use of automatic disintegration-detection instruments.

2.9.19. Particulate contamination: sub-visible particles

This text corresponds to the sign-off text signed by the Pharmacopoeial Discussion Group (PDG). The co-ordinating pharmacopoeia is the USP. Non-harmonised attributes are placed between black diamonds (♦ ♦), while local requirements only present in the Ph. Eur. text are placed between white diamonds (◊ ◊).

This text replaces the previous version published in Supplement 10.3 of the Ph. Eur., which contained an alternative procedure for both tests as a local requirement in the Ph. Eur., by a harmonised text mutually agreed upon by the PDG pharmacopoeias.

Introduction: reworded.

Method 1. Light obscuration count test: the alternative test procedure (which allows the use of sample volumes of less than 5 mL depending on instrument capability/sample properties) - now harmonised - has become the only test procedure. The text therefore no longer stipulates that, for preparations with a volume of less than 25 mL, at least 10 units must be combined, and the wording has been changed to state that a volume sufficient for a single test based on instrument capabilities and sample properties is to be used. A preference for testing single units has been added. The wording has been further clarified in several instances.

Method 2. Microscopic particle count test: the alternative test procedure – now harmonised – has become the only test procedure; as a result, the obligation to combine at least 10 units for small-volume preparations has been removed, allowing the use of fewer units depending on instrument capability and sample properties.

Evaluation (light obscuration and microscopic particle count tests): wording clarified.

2.9.54. Uniformity of delivered dose of inhalation and nasal preparations

This initial text has undergone bilateral harmonisation with the Japanese Pharmacopoeia (JP).

The procedures for testing the uniformity of delivered dose for some preparations for inhalation and nasal preparations have been transferred to this general chapter from the monographs on *Preparations for inhalation (0671)* and *Nasal preparations (0676)*. The acceptance criteria (partially harmonised for the various preparations) have been kept in the corresponding general monographs.

5.1.10. Guidelines for using the test for bacterial endotoxins

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14* and to expand the list of methods referred to in *2.6.14* to include the new method G.

5.1.13. Pyrogenicity

This general chapter has been revised as a consequence of the revision of general chapter *2.6.14. Bacterial endotoxins*, published in the same issue of the European Pharmacopoeia, to introduce the fluorimetric end-point method using recombinant factor C (rFC) as the new method G.

In this revised general chapter, the references to general chapter *2.6.32. Test for bacterial endotoxins* using recombinant factor C have been removed and a sentence has been added to highlight that considerations regarding sustainability should be made when choosing a method for the test for bacterial endotoxins.

5.32. Cell-based preparations for human use

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

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

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

5.36. mRNA vaccines for human use

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

5.37. Recombinant viral vectored vaccines for human use

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

5.39. mRNA substances for the production of mRNA vaccines for human use

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

5.40. DNA templates for the preparation of mRNA substances

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

GENERAL MONOGRAPHS

Gene therapy medicinal products for human use (3186)

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

Substances for pharmaceutical use (2034)

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

DOSAGE FORMS

Ear preparations (0652)

Ear sprays - Leak rate: as this test is generally applicable to all pressurised pharmaceutical preparations, it was added to the monograph *Pressurised pharmaceutical preparations (0523)* and deleted from the Ear sprays section of this monograph. The requirement to comply with the test is kept unchanged through the existing cross-reference to the monograph *0523* in the Definition section.

Nasal preparations (0676)

The procedures for intra-and inter-container testing of the uniformity of delivered doses have been transferred to a new general chapter entitled Uniformity of delivered dose of inhalation and nasal preparations (*2.9.54)* which has undergone bilateral harmonisation with the Japanese Pharmacopoeia (JP).

Leak rate: as this test is generally applicable for all preparations that are supplied in pressurised containers, it has been transferred to the monograph *Pressurised pharmaceutical preparations (0523)*.

Parenteral preparations (0520)

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

Preparations for inhalation (0671)

The procedures for intra- and inter-container testing of the uniformity of delivered doses have been transferred to a new general chapter entitled *Uniformity of delivered dose of inhalation and nasal preparations (2.9.54)* which has undergone bilateral harmonisation with the Japanese Pharmacopoeia (JP).

Leak rate: as this test is generally applicable for all preparations that are supplied in pressurised containers, it has been transferred to the monograph *Pressurised pharmaceutical preparations (0523)*. The requirement to comply with the test is kept unchanged through the existing cross-reference to the monograph *0523* in the Definition section.

Pressurised pharmaceutical preparations (0523)

Leak rate: test added for preparations supplied in pressurised metered-dose containers as it applies to all pressurised preparations.

Editorial changes have been made throughout the monograph to improve clarity and reflect current pharmacopeial style.

Veterinary semi-solid preparations for oral use (2638)

A revision proposal for this monograph was published in Pharmeuropa 34.3. In light of the comments received, the text has been further revised in many places and now includes the following changes compared to the monograph published in Ph. Eur. 11.3.

Latin title: molles replaced by semi solidae.

Production (describes mandatory requirements for manufacturers):

– tests to ensure the rheological properties of the preparation and the appropriate release of the active substance(s);

– a test to ensure the homogeneity of the preparation and to control the particle size when the preparation contains dispersed particles;

– a test for the uniformity of delivered mass within (intra) and between (inter) containers for metered-dose preparations supplied in multidose containers, with an example of inter-container mass uniformity testing (intra-container testing described in Tests section). The description of the intra-container testing has been expanded to cover cases in which the multidose container contains fewer than ten doses;

– a test for total delivered mass or volume – has been added.

Tests:

– an intra-container delivered mass uniformity test has been added;

– for preparations supplied in multidose containers, the test for uniformity and accuracy of delivered doses carried out on the minimum recommended dose, where the dose is usually expressed as mass; a limit for the maximum deviation of 10 per cent of the average dose from the minimum recommended dose has been set.

Labelling: the information required for preparations supplied in multidose and metered-dose containers has been added, together with the minimum recommended dose.

Editorial changes have been made throughout the monograph, including the Definition section, to improve clarity and reflect current pharmacopoeial style.

VACCINES FOR HUMAN USE

BCG for immunotherapy (1929)

Production: it has been clarified that the maximum length of the culture step (“not more than 21 days”) applies to each passage.

BCG vaccine, freeze-dried (0163)

Production: it has been clarified that the maximum length of the culture step (“not more than 21 days”) applies to each passage.

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

This monograph has been revised to take into account the control of pyrogenicity for the hexavalent vaccine containing haemophilus type b polysaccharide (Hib PRP) conjugated with Neisseria meningitidis group B outer membrane protein complex (OMP).

General provisions: a new sentence has been introduced to take into account the fact that, for bulk PRP conjugate, the carrier protein used may confound the results of the bacterial

endotoxin test (e.g. where PRP is conjugated to OMP). In such cases, with the agreement of the competent authority, the content of bacterial endotoxins may be determined for the PRP prior to conjugation only (as per monograph *1219* covering the haemophilus component) and the test may be omitted for the bulk PRP conjugate.

Final lot: the requirement for bacterial endotoxins test has been deleted, and the requirements for a test for pyrogenicity as described in the general monograph *Vaccines for human use (0153)* now apply.

The term 'free PRP' is now used consistently across the English text.

Tetanus vaccine (adsorbed) (0452)

Absence of tetanus toxin: a section on alternative *in vitro* methods to the test in guinea pigs has been added in the interest of animal welfare. This new section covers general considerations for alternative *in vitro* methods to encourage their use and describe prerequisites for their introduction as a replacement for the test in guinea pigs. The Binding And Cleavage ('BINACLE') method, which has been evaluated in a BSP collaborative study, is also included as an example of an *in vitro* method. The BINACLE method mimics essential steps of the mechanism of action of tetanus toxin and may be suitable to replace the test in guinea pigs, after product-specific validation to demonstrate that toxoids from the routine production process do not interfere with sensitive detection of tetanus neurotoxin.

For more information, see:

– *"Collaborative study for the characterisation of the BINACLE Assay for in vitro detection of tetanus toxicity in toxoids"* - Part 1;

– *"Collaborative study for the characterisation of the BINACLE Assay for in vitro detection of tetanus toxicity in toxoids*" - Part 2;

published in Pharmeuropa Bio & Scientific Notes in 2024.

The same changes have been introduced in the monograph on *Tetanus vaccine for veterinary use (0697)*.

Tetanus vaccine for veterinary use (0697)

Absence of tetanus toxin: a section on alternative *in vitro* methods to the test in guinea pigs has been added in the interest of animal welfare. This new section covers general considerations for alternative *in vitro* methods to encourage their use and describe prerequisites for their introduction as a replacement for the test in guinea pigs. The Binding And Cleavage ('BINACLE') method, which has been evaluated in a BSP collaborative study, is included as an example of an *in vitro* method. The BINACLE method mimics essential steps of the mechanism of action of tetanus toxin and may be suitable to replace the test in guinea pigs, after product-specific validation to demonstrate that toxoids from the routine production process do not interfere with sensitive detection of tetanus neurotoxin.

For more information, see:

– *"Collaborative study for the characterisation of the BINACLE Assay for in vitro detection of tetanus toxicity in toxoids"* - Part 1;

– *"Collaborative study for the characterisation of the BINACLE Assay for in vitro detection of tetanus toxicity in toxoids"* - Part 2;

published in Pharmeuropa Bio & Scientific Notes in 2024.

The same changes have been introduced in the monograph on *Tetanus vaccine (adsorbed) (0452)*.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Frangula bark (0025)

Definition: botanical names updated; limit for content widened and now refers to total hydroxyanthracene glycosides instead of glucofrangulins, in accordance with the new assay.

Identification: test C (TLC) replaced by a new, more specific HPTLC procedure in accordance with general chapter *2.8.25*, using *HPTLC system suitability solution CRS* for the system suitability test, that is able to detect the main hydroxyanthracene glycosides characteristic of the herbal drug and presents a fingerprint distinct from other herbal drugs containing hydroxyanthracene glycosides such as cascara; test D, which is able to detect anthraquinones by colorimetry, deleted since it does not provide added value for the purpose of identification relative to the new test C by HPTLC.

Other species of Rhamnus; anthrones: test deleted since it has become obsolete. On the one hand, no significant adulterants, even from other species of Rhamnus, are known for this herbal drug. On the other hand, a test for anthrone content is not considered necessary because, according to the literature, the presence of anthrones has long been described in the freshly harvested herbal drug before drying and storage, and high anthrone content is associated with low hydroxyanthracene glycoside content, which would be detected by the new assay procedure.

Total anthraquinones (emodin, chrysophanol and physcion): new HPLC procedure added, covering the control of the main anthraquinone aglycones in this herbal drug (i.e. emodin, chrysophanol and physcion). Anthraquinone aglycone content is considered to be an important quality parameter, since aglycone content may increase during storage and processing of the herbal drug due to the degradation of hydroxyanthracene glycosides present in the herbal drug. Therefore, the limit for total anthraquinones is expressed as a maximum per cent value, calculated with reference to the sum of total hydroxyanthracene glycosides and total anthraquinones.

Assay: unspecific spectrophotometric method replaced by a new and specific HPLC procedure able to quantitate the eight main hydroxyanthracene glycosides present in the herbal drug. These compounds are classified as constituents with known therapeutic activity, which contribute substantially to the overall therapeutic activity of the herbal drug.

Frangula bark dry extract, standardised (1214)

Definition: limit for content modified and now refers to total hydroxyanthracene glycosides instead of glucofrangulins, in accordance with the new assay.

Identification: test A (TLC) replaced by a new, more specific HPTLC procedure in accordance with general chapter *2.8.25*, using *HPTLC system suitability solution CRS* for the system suitability test, that is able to detect the main hydroxyanthracene glycosides characteristic of the extract and presents a fingerprint distinct from other extracts containing hydroxyanthracene glycosides such as cascara dry extract, standardised; test B, which is able to detect anthraquinones by colorimetry, deleted, since it does not provide added value for the purpose of identification relative to the new HPTLC test, which is able to detect the main hydroxyanthracene glycosides in the extract.

Total anthraquinones (emodin, chrysophanol and physcion): new HPLC procedure added, covering the control of the main anthraquinone aglycones in this extract (i.e. emodin, chrysophanol and physcion). Anthraquinone aglycone content is considered to be an important quality parameter, since aglycone content may increase during storage of the

extract and as a consequence of the processing of the corresponding herbal drug, due to the degradation of hydroxyanthracene glycosides present in the herbal drug. Therefore, the limit for total anthraquinones is expressed as a maximum per cent value, calculated with reference to the sum of total hydroxyanthracene glycosides and total anthraquinones.

Assay: unspecific spectrophotometric method replaced by a new and specific HPLC procedure able to quantitate the eight main hydroxyanthracene glycosides present in the extract. These compounds are classified as constituents with known therapeutic activity which contribute substantially to the overall therapeutic activity of the extract.

Labelling: section updated according to the changes introduced in the assay and definition.

Goldenrod (1892)

Definition: limit for content widened based on data from recent batches.

Guar (1218)

Identification: in test A, reference to general chapter *2.8.23. Microscopic examination of herbal drugs* introduced; in test D, TLC replaced by HPTLC in accordance with general chapter *2.8.25*, preparation of the test solution optimised, reagent used to treat the plate modified, fourth reference substance added.

Tragacanth, sterculia gum, agar, alginates and carrageenan: addition of reference to general chapter *2.8.23*, whereby the preparation is “washed” with water after about one minute of contact with the dye. This extra step improves the reproducibility of the test (cell walls expected to appear colourless or pale pink, the gum pink, and the mucilage from tragacanth, sterculia gum, agar, alginates or carrageenan, if present, would stain red).

Nettle leaf (1897)

Identification: test A updated to take account of the differences between *Urtica dioica* and *U. urens* (as test B does not discriminate between the two species since no significant differences are observed under the microscope between *U. dioica* and *U. urens*); in test B, sieve number of 500 (*2.9.12*) prescribed for analysis of the powdered herbal drug; test C replaced by HPTLC procedure in accordance with general chapter *2.8.25*, *HPTLC system suitability solution CRS* used for the system suitability test and separate acceptance criteria introduced for *U. dioica* and *U. urens*.

Nettle root (2538)

Definition: hybrids of *Urtica dioica* L. and *Urtica urens* L. excluded as these are not known to exist.

Identification A and B: updated to take account of the differences between *U. dioica* and *U. urens*.

Identification B: sieve number of 500 (*2.9.12*) prescribed for analysis of the powdered herbal drug; illustration of powdered herbal drug introduced and its legend integrated into text of identification B.

Identification C: a new test procedure, based on HPTLC in accordance with general chapter *2.8.25*, has been introduced; it relies on the amino-acid content of the herbal drug and it uses the *HPTLC system suitability solution CRS* for the system suitability test.

White mulberry leaf (3164)

Identification test C: the requirement stating that zone (h) must be more intense than zone (j) has been moved from the table to the 'Results B' section in order to facilitate the assessment of the results.

MONOGRAPHS

Amoxicillin sodium (0577)

Content: the lower limit has been adjusted following the introduction of new impurity limits.

Production: as some manufacturers may choose no longer to use *N,N*-dimethylaniline in their production process, the presence of this impurity is now controlled using a risk-based approach. As this aspect cannot always be verified by an independent analyst, the requirement for testing *N,N*-dimethylaniline has been removed from the Tests section and a Production section has been introduced.

Identification: a new *amoxicillin sodium CRS* has been introduced in test A (infrared absorption spectrophotometry); test C (colour reaction) has been deleted; reaction (a) of sodium (former test D) has been replaced by reaction (b) as the latter is easier to perform whereas the former requires intensive rubbing of the inside of the test tube with a glass rod to form the precipitate; the reaction of sodium has been deleted from the first identification series as test A (infrared absorption spectrophotometry) is now considered sufficient to distinguish amoxicillin sodium from amoxicillin trihydrate.

Specific optical rotation: the test has been deleted as purity is sufficiently controlled by the new related substances LC method.

Related substances, Assay: an improved LC method capable of separating additional impurities has been introduced; limits have been set for the newly specified impurities and the limit for total impurities has been reduced based on current batch data; the system suitability criteria pertaining to selectivity are now clearly indicated in the assay (previously applied as part of the test for related substances).

N,N-Dimethylaniline: see Production section above.

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

Impurities: additional impurities have been included.

Amoxicillin trihydrate (0260)

Content: the lower limit has been adjusted following the introduction of new impurity limits.

Production: as some manufacturers may choose no longer to use *N,N*-dimethylaniline in their production process, the presence of this impurity is now controlled using a risk-based approach. As this aspect cannot always be verified by an independent analyst, the requirement for testing *N,N*-dimethylaniline has been removed from the Tests section and a Production section has been introduced.

Identification: test C (colour reaction) has been replaced by a reference to the pH test as the latter makes it possible to discriminate between the trihydrate form and the sodium salt.

Specific optical rotation: the test has been deleted as purity is sufficiently controlled by the new related substances LC method.

Related substances, Assay: an improved LC method capable of separating additional impurities has been introduced; limits have been introduced for specified impurities and for total impurities based on current batch data; the system suitability criteria pertaining to selectivity are now clearly indicated in the assay (previously applied as part of the test for related substances).

Storage: the statement has been updated to include situations where the substance is sterile.

Impurities: additional impurities have been included.

Betacarotene (1069)

Loss on drying: test replaced by a micro-determination of water test; considering the relevant residual solvent (i.e. acetone) was not properly controlled by the loss on drying test, residual water is tested separately and acetone is now covered by the requirements for residual solvents as described in the general monograph *Substances for pharmaceutical use (2034)*.

Assay: system suitability criteria pertaining to selectivity now clearly indicated in this test (previously applied as part of the test for related substances).

Biotin (1073)

Identification test B: particle size requirement removed.

Related substances: in the preparation of the test solution, mass expressed using more significant figures due to the quantitative use of this solution.

Carnauba wax (0597)

Identification: thin-layer chromatography procedure replaced by infrared absorption spectrophotometry procedure, which is a quicker, more precise technique that uses fewer solvents.

Chlorpromazine hydrochloride (0475)

Characters: solubility in heptane added.

Identification: in test A (IR), description of sample preparation deleted so as not to limit possible modes of sample preparation; recrystallisation procedure added since the substance shows polymorphism.

Impurity F: TLC test deleted as it is obsolete with the proposed HPLC procedure for related substances, which now covers impurity F, allowing the quantitative determination of this impurity.

Related substances: a new quantitative HPLC test is proposed, which now covers impurity F and an additional five new impurities. The new method does not require the solutions to be prepared immediately before use, the system suitability test is based on the critical separation between impurity F and chlorpromazine, it includes an ethylene-bridged pentafluorophenylpropylsilyl silica gel based stationary phase, it replaces the cumbersome buffer solution by a perchloric acid solution, and it introduces a gradient for the mobile phase. Moreover, the impurity limits have been updated to reflect the quality of substances in approved medicinal products on the European market, hence all known impurities are listed

as unspecified impurities with a limit of maximum 0.10 per cent each, and a limit for total impurities of maximum 0.3 per cent is included.

Assay: concentration of solution of hydrochloric acid used expressed in g/L instead of M (mol/L); users are therefore not obliged to standardise this solution before use.

Impurities: section updated in accordance with revised test for related substances.

Dextromethorphan hydrobromide monohydrate (0020)

Acidity or alkalinity: it is now clearly indicated that the solution may also turn pink.

2,4-Dichlorobenzyl alcohol (2410)

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

Water: change of the procedure (i.e. direct sample introduction instead of the evaporation technique).

Assay: system suitability criteria pertaining to selectivity now clearly indicated in this test (previously applied as part of the test for related substances).

Dodecyl gallate (2078)

Content: limits updated to reflect change of analytical procedure used for the assay.

Identification: infrared absorption spectrophotometry (IR) test introduced; identification by thin-layer chromatography (TLC) deleted as it does not provide added value relative to IR and melting point.

Related substances: TLC test for gallic acid (impurity A) replaced by liquid chromatography (LC) test for related substances; limit for impurity A tightened; limit for total impurities and reporting threshold added; limit for unspecified impurities of maximum 0.3 per cent added.

As this substance is used in medicinal products as an excipient (antioxidant, preservative), the thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for Pharmaceutical use (2034)* do not apply.

Assay: ultraviolet absorption spectrophotometry procedure replaced by LC used for related substances.

Impurities: section updated in accordance with the new limit for impurity A.

Doxazosin mesilate (2125)

Identification: an alternative and user-friendly recrystallisation procedure is proposed, which does not require heating under a reflux condenser for 3 h nor a large amount of sample – the previous recrystallisation procedure required about 500 mg of the CRS in order to have a sufficient volume of solution to be condensed in a reflux apparatus (e.g. 5 mL if using a 25 mL round-bottom flask), whereas each vial of *doxazosin mesilate CRS* contains only about 60 mg of substance.

Assay: system suitability criterion pertaining to resolution now indicated (previously applied only as part of the test for related substances).

Erythropoietin concentrated solution (1316)

Glycan analysis, Polyacrylamide gel electrophoresis and immunoblotting, Peptide mapping, Capillary zone electrophoresis: in order to ensure the provision of a standard suitable for the intended purpose, e*rythropoietin for physicochemical tests CRS* has been replaced by two new CRSs: *erythropoietin for glycan analysis, peptide mapping & SDS-PAGE/immunoblotting CRS* (Glycan analysis, polyacrylamide gel electrophoresis and immunoblotting and Peptide mapping tests) and *erythropoietin for CZE CRS* (Capillary zone electrophoresis test).

Felodipine (1013)

First identification: test relabelled due to changes in the second identification.

Second identification: former tests A and B (by UV) deleted since not feasible in pharmacies, new test A (by melting point) introduced; test C relabelled (formerly D).

Related substances: *in situ* preparation of impurity A transferred from the former identification test B.

Golimumab injection (3187)

Latin subtitle added.

Haemodialysis solutions, concentrated, water for diluting (1167)

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

Histamine dihydrochloride (0143)

Content: lower limit revised in accordance with the Technical Guide.

First identification: former test D relabelled as test C due to changes in the second identification.

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

Second identification: in test B (by TLC), description of the analytical procedure transferred from the Tests section, mobile phase modified to avoid the use of acetonitrile (uncommon solvent for pharmacies) and '*TLC silica gel G plate R*' replaced by '*TLC silica gel plate R*'; former test C deleted as considered not necessary for the purpose of the second identification.

pH: values rounded to 2 significant figures.

Related substances: new analytical procedure by liquid chromatography introduced to replace the TLC procedure for histidine (impurity A). This new procedure also covers an additional impurity. Limits and reporting threshold set based on the requirements of general monograph *2034*, on approved specifications and on available batch data.

Loss on drying: sample size increased from 0.20 g to 1.000 g.

Impurities: transparency list introduced; two impurities now described.

Editorial changes made throughout the monograph.

Hyoscine hydrobromide hydrate (0106)

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

Definition/structure/formula: updated according to new title.

Characters: the statement "It shows polymorphism (*5.9*)." has been introduced.

Related substances: liquid chromatography procedure transformed into a quantitative test where all impurities are quantified with respect to the concentration of hyoscine hydrobromide hydrate; limits updated based on data from manufacturers and the requirements of general monograph *2034* (impurities A, C and D listed as unspecified impurities and limit for unspecified impurities introduced); grade of a solvent amended in accordance with the Technical Guide; in the preparation of reference solution (c), volumes expressed using fewer significant figures due to the qualitative use of this solution; symmetry factor requirement deleted.

Isoniazid (0146)

Identification: test B (mixed melting point) introduced for the second identification; test by IR (formerly test B) relabelled as test C due to this addition; former test C deleted as, according to comments from users, decomposition instead of melting is observed at the described temperature. For the purpose of the second identification, test A (melting point) replaced by the newly introduced test B.

Ivermectin (1336)

Related substances: the test now has to be carried out protected from light to prevent the degradation of impurity M, which has been newly introduced; a new CRS and corresponding reference solution (e) allowing the identification of impurity peaks have been introduced, as well as information concerning the relative retentions of these impurities; system suitability requirements and limits have been revised.

Ethanol and formamide: the internal standard solution is now added earlier to compensate for extraction losses; the content of these solvents now has to be determined using a one-point calibration method.

Storage: the statement has been amended since the substance is also available in sterile grade.

Labelling: a new section has been introduced.

Impurities: new impurities have been introduced.

Kanamycin monosulfate monohydrate (0032)

Title: the Latin title has been corrected.

Lercanidipine hydrochloride (3052)

Loss on drying: this test has been replaced by a semi-micro determination of water test in view of additional data from approved manufacturers in Europe and experimental work.

The limit has been amended to take into account levels of water in substances in approved medicinal products on the European market.

Assay: system suitability criteria pertaining to selectivity now clearly indicated in this test (previously applied as part of the test for related substances).

Levothyroxine sodium hydrate (0401)

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

Related substances: in the preparation of reference solution (d), volume and mass expressed using fewer significant figures due to the qualitative use of this solution; grade of solvents amended in accordance with the Technical Guide.

Assay: system suitability criteria pertaining to selectivity now clearly indicated in this test (previously applied as part of the test for related substances).

Impurities: structure of impurity G introduced.

Linseed oil, virgin (1908)

Cadmium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted from the monograph. The values reported in batch data from manufacturers over the past decade were all below the limit of quantitation (0.07 ppm). As is the case with other oilseeds, linseed can accumulate cadmium from the soil if the latter contains elevated levels but cadmium contamination in oil obtained by cold expression is unlikely since cadmium is predominantly attached to other parts of the seed (particularly cell walls and proteins) rather than the oil.

Identification test A: reference to Figure 2.3.2.-2 added as either method A or method B can be performed.

Composition of fatty acids: clarification that the specification refers to total fatty acids with chain length less than C_{16} introduced.

Manganese gluconate (2162)

CAS number: CAS number has been added.

Definition: a statement indicating that the monograph refers to both water-free and hydrate forms has been added.

Zinc: the preparation of the test and standard solutions has been modified to increase the sensitivity of the test.

Methylthioninium chloride hydrate (1132)

Assay: the concentrations of the test and reference solutions have been decreased to 0.05 mg/mL to improve the symmetry of the peaks due to methylthioninium obtained in the chromatograms of these solutions. As a result, the system suitability test requirement of maximum peak symmetry of 3.0 has been deleted and the tighter requirement prescribed in general chapter *2.2.46* (i.e. 0.8 to 1.8) now applies. System suitability criterion pertaining to resolution now indicated (previously applied as part of the test for related substances).

Metoclopramide (1348)

Impurity E: CRS for impurity E is used as the external reference standard instead of its reagent; the concentrations of the test solution and of the reference solution containing impurity E have been increased in order to achieve sufficient sensitivity; the system suitability test has been added with detection at 254 nm.

Metoclopramide hydrochloride monohydrate (0674)

Impurity E: CRS for impurity E is used as the external reference standard instead of its reagent; the system suitability test has been added with detection at 254 nm.

Nilotinib hydrochloride monohydrate (2993)

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

Impurity A: test deleted because, according to recently received data, the impurity is not mutagenic and can be controlled by the related substances test at the limit for unspecified impurities.

Assay: system suitability criteria pertaining to selectivity now clearly indicated in the test procedure (previously applied as part of the test for related substances).

Octyl gallate (2057)

Content: limits updated to reflect change of analytical procedure used for the assay.

Identification: infrared absorption spectrophotometry (IR) test introduced; identification by thin-layer chromatography (TLC) deleted as it does not provide added value relative to IR and melting point.

Related substances: TLC test for gallic acid (impurity A) replaced by liquid chromatography (LC) test for related substances; limit for impurity A tightened; limit for total impurities and reporting threshold added; limit for unspecified impurities of maximum 0.3 per cent added.

As this substance is used in medicinal products as an excipient (antioxidant, preservative), the thresholds indicated under Related substances (Table 2034.-1) in the general monograph *Substances for Pharmaceutical use (2034)* do not apply.

Assay: ultraviolet absorption spectrophotometry procedure replaced by LC used for related substances.

Impurities: section updated in accordance with the new limit for impurity A.

Paclitaxel (1794)

Related substances (tests A and B): requirements for specific surface area and pore size of the column deleted.

Assay: system suitability criteria pertaining to selectivity now clearly indicated in this test (previously applied as part of the test for related substances).

Penbutolol sulfate (1461)

Related substances: limits updated based on the requirements of general monograph *2034*; in the preparation of reference solution (a), volumes and mass expressed using fewer significant figures due to the qualitative use of this solution; reference solution (b) now

prepared at a concentration corresponding to 0.1 per cent of the concentration of the test solution; former reference solution (c) deleted and disregard limit now determined using reference solution (b); grade of solvents amended in accordance with the Technical Guide.

Pentamidine diisetionate (1137)

Identification (IR): preparation of the discs deleted.

Related substances: reagent used to describe stationary phase modified; liquid chromatography procedure transformed into a quantitative test where all impurities are quantified with respect to the concentration of pentamidine diisetionate; concentration of the solution used for quantitation lowered from 0.2 per cent to 0.1 per cent; reporting threshold and limits updated based on manufacturers' data and the requirements of the general monograph *2034*.

Piperacillin monohydrate (1169)

Impurities : the trivial name of impurity H has been corrected.

Salbutamol sulfate (0687)

Related substances: the correction factor (i.e. 1/RRF) of impurity Q versus salbutamol sulfate at 273 nm is about 0.07 and manufacturers have reported overestimated levels of impurity Q exceeding the 0.10 per cent limit when using the current test for related substances; hence, a new reference solution containing *salbutamol impurity Q CRS* at 0.10 per cent is introduced in order to quantitate the content of impurity Q against this reference standard.

Impurities: impurity Q listed as specified according to the changes introduced in the test for related substances.

Sitagliptin phosphate tablets (2927)

Related substances: based on data provided by a generic manufacturer on their approved product, the limit for total impurities has been relaxed.

Assay: system suitability criteria pertaining to selectivity now clearly indicated in this test (previously applied as part of the test for related substances).

Sultamicillin (2211)

Production: as methyl toluene sulfonate is genotoxic and has been identified as a potential impurity, this section has been introduced to alert about the potential risk of contamination. In consistency with other similar monographs, reference is made to general chapter *2.5.40* to support manufacturers in their control strategy.

Related Substances: reagent used to describe stationary phase modified; grades of solvents amended in accordance with the Technical Guide (2022).

Assay: system suitability criteria pertaining to selectivity are now clearly indicated in this test (previously applied as part of the test for related substances).

Editorial changes made throughout the monograph.

Thiamazole (1706)

Second identification: former test B (by UV) is not feasible in all pharmacies and has been replaced by a mixed melting point test; test A (by melting point) has been removed from the second identification; test D (by TLC) has been deleted to avoid exposure to iodine vapour and iodine is not a reagent commonly used by pharmacies.

Trimetazidine dihydrochloride (1741)

Identification: Ph. Eur. reference spectrum replaced by a reference substance.

Related substances: all impurities other than impurity B now covered by the explicit criterion for unspecified impurities to reflect the quality of substances in approved medicinal products on the European market.

Impurities: section has been updated.

Water for injections (0169)

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.

Water, purified (0008)

The inclusion of the recombinant Factor C (rFC) test as method G in general chapter *2.6.14. Bacterial endotoxins* renders general chapter *2.6.32. Test for endotoxins using recombinant factor C* obsolete and the chapter has therefore been suppressed from the Ph. Eur. (Issue 13.1). The purpose of this revision was to delete the reference to *2.6.32* since the contents of that chapter are now included in *2.6.14*.