Comments concerning texts published in Supplement 11.1

Brief descriptions of the modifications that have been made to new, revised and corrected texts adopted by the European Pharmacopoeia Commission at the March session and published in Supplement 11.1 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 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

2.2.27. Thin-layer chromatography

Terminology: updated to reflect current terminology for general chapters.

Procedure: Revised general chapter *2.2.46* no longer restricts the objective of adjustments of chromatographic conditions to cases where the system suitability criteria cannot be met with the original chromatographic conditions. However, these criteria must still be met if an adjustment is made. Since the paragraph applies both to non-quantitative and quantitative procedures, it has been moved under this section.

Visual evaluation, Identification: clarification of the statement regarding performance of the plate and system suitability.

2.2.28. Gas chromatography

Procedure: Revised general chapter *2.2.46* no longer restricts the objective of adjustments of chromatographic conditions to cases where the system suitability criteria cannot be met with the original chromatographic conditions. However, these criteria must still be met if an adjustment is made.

2.2.29. Liquid chromatography

Procedure: Revised general chapter *2.2.46* no longer restricts the objective of adjustments of chromatographic conditions to cases where the system suitability criteria cannot be met with the original chromatographic conditions. However, these criteria must still be met if an adjustment is made.

2.2.30. Size-exclusion chromatography

Procedure: Revised general chapter *2.2.46* no longer restricts the objective of adjustments of chromatographic conditions to cases where the system suitability criteria cannot be met

with the original chromatographic conditions. However, these criteria must still be met if an adjustment is made.

2.2.45. Supercritical fluid chromatography

Terminology: updated to reflect current terminology for general chapters.

Procedure: Revised general chapter *2.2.46* no longer refers to supercritical fluid chromatography; hence the paragraph under Procedure is omitted.

2.6.17. Test for anticomplementary activity of immunoglobulin

Deletion of the sentences stating that stabilised sheep blood and antiserum against sheep red blood cells are available from a number of commercial sources: it is acceptable to use assay components prepared in-house or from a commercial source, however, the EDQM cannot recommend commercial reagents or provide information on potential suppliers.

2.7.26. Cell-based assays for potency determination of TNF-alpha antagonists

This general chapter describes in detail the execution of four specific cell-based assay procedures (representative of bioassays commonly used to determine the potency of TNF-alpha antagonists) and provides considerations on data analysis, system suitability, assay acceptance criteria and results evaluation. General recommendations on adjustment of assay conditions are also given. It does not exclude the use of alternative procedures that are acceptable to the competent authority. The chapter is the result of extensive experimental work undertaken by a large number of laboratories, to verify the applicability of various bioassays as multi-product procedures suitable to assess the TNF-alpha inhibitory effect.

Rationalisation of these cell-based assays will contribute to standardising the different TNF-alpha antagonists available and in development.

2.8.2. Foreign matter

The requirements for other foreign elements like moulds, insects and other animal contamination have been further specified.

2.9.5. Uniformity of mass of single-dose preparations

Table 2.9.5.-1 expanded to include additional dosage forms that refer to this general chapter.

2.9.38. Particle-size distribution estimation by analytical sieving

This minor revision corresponds to Revision 1, Correction 1 (based on PDG working procedure) within the Pharmacopoeial harmonisation process (Ph. Eur., JP, USP). The coordinating pharmacopoeia is the JP.

This minor revision to the diameters of the test sieves takes into account the standard diameters described in international guidelines (e.g. ISO, ASTM, JIS). The general chapter now includes test sieve diameters of 200 mm and 203 mm (8 inches) as well as 75 mm and 76 mm (3 inches).

3.2.9. Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders

The general revision of the general chapter included changes to the following:

Definition and scope: use of natural rubber latex not permitted but dry natural rubber may be used.

Identification: IR, which may in itself be selective, maintained as the main and basic technique for rubber identification; status of the Total ash test changed from always necessary to only possibly needed and complementary; other potential techniques listed.

Acidity or alkalinity: guidance on how to choose titrant added.

Absorbance: filtration only needed for turbid or hazy solutions.

Extractable heavy metals: deleted to align with ICH Q3D and Ph. Eur. policy on elemental impurities.

Functional tests: introduction expanded to clarify cases in which the tests for penetrability, fragmentation and self-sealing may have to be adapted or can be omitted.

Fragmentation: specific testing procedure for closures used for dry preparations removed. Allowing the sample to stand for 16 h at room temperature proved unnecessary and this requirement has therefore been deleted from the procedure.

Editorial changes have been made throughout the general chapter.

5.2.2. Chicken flocks free from specified pathogens for the production and quality control of vaccines

A designated SPF flock is derived from chickens shown to be free from the agents listed in Table 5.2.2-1. Following the revision, published in Supplement 10.2, of chapter *5.2.5. Management of extraneous agents in IVMPs to include a list of extraneous agents* in an annex, this table has been updated to add:

- Avian rotavirus: because faecal contamination of the shell could result in transmission to the embryo and then to the birds, this agent is listed in chapter *5.2.5* Annex 1 (AVIAN (Poultry) - main list) and should therefore also be included in the table below, even if no vertical transmission has been demonstrated, and

- Fowl-pox virus: most of the poxviruses can be ruled out by clinical observation and examination of the flocks as well as post-mortem examination (see below under ROUTINE TESTING OF DESIGNATED SPF FLOCKS/General examination and necropsy). However, an immunoassay may also be used as it could detect a contamination at an earlier stage and this would harmonise the current practices. Therefore this agent, which has always been tested for routinely by clinical examination but also by serological testing by some manufacturers, is added to Table 5.2.2-1 below.

5.21. Chemometric methods applied to analytical data

General chapter completely rewritten and updated in view of the latest developments. This general revision mainly includes:

- an update of section 1. General aspects with a review of parts on Pre-processing (1-2- 2-6) and Assessment and validation of chemometric methods (1-3);

- new sub-sections on Independent component analysis (2-2) and Decision trees and random forests (2-6);

- general review of sub-sections on Similarity measures (2-3), Clustering (2-5), Multiple linear regression (2-8), Principal component regression (2-9), Support vector machines for supervised classification (2-11) and Artificial neural networks (2-12);

- a new section 3. Related application fields, including sub-sections on Chemometrics in chemical imaging (3-1) and Data fusion (3-2);

- an update of the Glossary (i.e., definition of β-distribution deleted and definitions of parameter and hyperparameter introduced) and the Abbreviations.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs published in Supplement 11.1.

GENERAL MONOGRAPHS

Radiopharmaceutical preparations (0125)

This general monograph on Radiopharmaceutical preparations has undergone a global revision and update, including editorial modifications and the following:

Definitions: clarification with respect to the monograph's scope including how to deal with radionuclide precursors used in continuous processes and which are therefore unavailable for testing.

Paragraphs on Radionuclidic purity, Radiochemical purity and Chemical purity have been merged with the respective sections under "Tests". Outdated and irrelevant terminology has been deleted ("carrier-free preparation", "no carrier added preparation"). The term "molar radioactivity" has been added, as well as an explanation of the statement "maximum recommended dose in millilitres (V)".

Production section: updated to reflect current state-of-the-art radionuclide production methods and to include information on chemical precursors and excipients. General textbook information has been deleted.

Identification: clarification that a radionuclide is identified by its half-life or nature and energy of its radiation or both.

pH, Elemental impurities and Particulate contamination: introduction of sections.

Non-radioactive substances and related substances: expansion of the section explaining how potential impurities are to be considered.

Sterility: the section has been grouped with the other tests not involving radioactivity measurement and has been expanded to allow omission of a pre-filtration filter integrity test and to include the requirements for radionuclide precursors.

Physiological distribution: the section has been grouped with the other tests not involving radioactivity measurement. The part on the performance of the test has been removed as, in-line with the 3R principles, the test should no longer be used. However, it had been accepted

that certain monographs for radiopharmaceutical preparations still prescribed the test. Due to the small numbers of these preparations used in practice, cross-validation of alternative tests would consume more animals than the continuation of the test for many years. These monographs contain test details.

Bacterial endotoxins: changes to the section to indicate that limits for radionuclide precursors must allow for contributions from other sources in the production of radiopharmaceuticals.

Radionuclidic purity: removal of the half-life test and inclusion of an approximate half-life test as a contributor to the Identification of positron-emitting radionuclides.

Clarification that preparations made from radionuclide precursors must comply with the precursor's radionuclidic purity requirements throughout the shelf life of the final preparation.

Radioactivity: section added to explain that in case no Ph. Eur. monograph exists, limits are to be defined and justified.

Labelling: additions have been made to the section.

DOSAGE FORMS

Vaginal preparations (1164)

Production: control of particle size moved to general production section and deleted from individual production sections.

Tests:

- Uniformity of dosage units: clarification that in the case of liquid and semi-solid vaginal preparations, the test applies only to preparations that are supplied in single-dose containers and intended for systemic effect,

- Dissolution: wording aligned with that of other monographs, such as Tablets (0478).

Definitions: aligned with Standard Terms, where possible.

Vaginal delivery systems: new section.

VACCINES FOR VETERINARY USE

Avian infectious bronchitis vaccine (live) (0442)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Avian infectious bursal disease vaccine (live) (0587)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Avian infectious encephalomyelitis vaccine (live) (0588)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Avian infectious laryngotracheitis vaccine (live) (1068)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Avian viral tenosynovitis vaccine (live) (1956)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Duck viral hepatitis type I vaccine (live) (1315)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Fowl-pox vaccine (live) (0649)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Infectious chicken anaemia vaccine (live) (2038)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Newcastle disease vaccine (live) (0450)

3-2. Bacteria and fungi. No repetition of the details of the requirements for microbiological quality as stated in the general monograph *Vaccines for veterinary use (0062)*.

Rabies vaccine (inactivated) for veterinary use (0451)

2-4-4. Batch potency test. As a 3Rs commitment, the NIH test is reserved for development and qualification of standards/reference preparations only and not used anymore as a routine batch potency test.

3-3. Residual live virus. This test was previously performed at the final product stage either by an *in vitro* test using a cell culture (for non-adjuvanted vaccines) or by an *in vivo* test using mice injected intracerebrally (for adjuvanted vaccines). Both tests are deleted because they are redundant with the test for residual live virus (2-4-1) performed in process. Production under GMP conditions and validated production processes to demonstrate consistency combined with the history of safe use of the products approved in Europe support the proposal to delete the *in vivo* test for residual live virus on the final product. A product which is tested at the in process stage does not need to be tested again at the final product stage, especially since there is no reversion to virulence. However, if the test still has to be

performed, owing to the 3Rs commitment, it is no longer acceptable to use an *in vivo* test. Only a suitable *in vitro* test can be used. For adjuvanted vaccines, instruction is given to either separate the adjuvant from the liquid phase, by a method that does not inactivate the virus or otherwise interfere with the detection of live viruses, or to carry out a test for inactivation on the mixture of bulk antigens before addition of the adjuvant.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Flumazenil (*N*-[^{11}C]methyl) injection (1917)

It has been shown that determination of the radioactive half-life of ^{11}C- and ^{15}O-radiopharmaceutical preparations cannot be used as a test for radionuclidic purity with the required sensitivity. There is also no scientific rationale for the determination of individual radionuclidic impurities in preparations containing these radionuclides produced from a gaseous target. Determination of the approximate half-life does however contribute to the identification of the radionuclide.

In view of the above, the Identification and Radionuclidic purity sections have been revised. Other editorial changes have also been made for harmonisation purposes.

The MOLECULAR FORMULA and the RELATIVE MOLECULAR MASS have been added.

Definition: the Content statement has been changed to that in The Guide for the Elaboration of Monographs on Radiopharmaceutical Preparations.

Production: details of the RADIONUCLIDE PRODUCTION and RADIOCHEMICAL SYNTHESIS are transferred to the knowledge database in-line with current practice for monographs on PET preparations. It is prescribed that the radionuclide is derived from a gaseous target. The quality of chemical precursors is covered by the general monograph *Chemical precursors for radiopharmaceutical preparations (2902)*. The tests for demethylflumazenil have thus been deleted from this specific monograph.

Identification: approximate half-life has been included and the wording of the other identification tests has been harmonised across the ^{11}C-monographs.

RADIONUCLIDIC PURITY:

The established standard methods for production of carbon-11 use the ^{14}N(p,α)^{11}C nuclear reaction by proton bombardment of a nitrogen/hydrogen or nitrogen/oxygen target gas mixture producing either [^{11}C]methane or [^{11}C]carbon dioxide respectively. With these methods no measurable amounts of long-lived radionuclide impurities are formed in the target material. Theoretically fluorine-18 in the form of [^{18}F]fluoride could be formed by the ^{18}O(p,n)^{18}F nuclear reaction on oxygen-18 in the target gas. However, no measurable amounts of fluorine-18 are formed due to the low concentration (0.2 per cent) of oxygen-18 in the trace amounts of oxygen in the target gas. Furthermore, any [^{18}F]fluoride ion formed is deposited on the target holder. Depending on the material in the foil separating the cyclotron from the target material long-lived metallic radionuclides could be formed, especially if Havar foils are used. However, these radionuclides are cationic metals and not transferred into the target gas.

They are thus quantitatively retained in the foil. The primary carbon-11 precursors formed in the target gas, [^{11}C]methane or [^{11}C]carbon dioxide, are subjected to purification and further chemical transformation to radiopharmaceuticals before use. Considering the above there is no scientific rationale for the determination of individual radionuclidic impurities in carbon-11 radiopharmaceuticals and the test for radionuclidic purity is therefore solely an examination of the gamma-ray spectrum.

Labelling: the Labelling section has been removed because these details appear in the general monograph on *Radiopharmaceutical preparations (0125)*.

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

Identification B: the limits for the approximate half-life test have been set with a tolerance of ± 10 per cent, which is considered more reasonable in view of the short half-life of gallium-68.

Sterility: inclusion of a test in case of use of the solution in e.g. radiopharmaceutical kits, which have no further sterilisation process before administration to the patient.

Bacterial endotoxins: revision of the limit to take account of the fact that accelerator-produced gallium (^{68}Ga) chloride for radiolabelling is not directly for patient use but used for the preparation of injectable radiopharmaceutical preparations. Bacterial endotoxins from other sources can be present in the final preparation to be administered to the patient. Bacterial endotoxins are limited per batch produced, instead of per maximum volume of a patient dose. As a consequence, 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.

L-Methionine ([^{11}C]methyl) injection (1617)

It has been shown that determination of the radioactive half-life of ^{11}C- and ^{15}O-radiopharmaceutical preparations cannot be used as a test for radionuclidic purity with the required sensitivity. There is also no scientific rationale for the determination of individual radionuclidic impurities in preparations containing these radionuclides produced from a gaseous target. Determination of the approximate half-life does however contribute to the identification of the radionuclide.

In view of the above, the Identification and Radionuclidic purity sections have been revised. Other editorial changes have also been made for harmonisation purposes.

The MOLECULAR FORMULA and the RELATIVE MOLECULAR MASS have been added.

Definition: the Content statement has been changed to that in The Guide for the Elaboration of Monographs on Radiopharmaceutical Preparations and the purity statements have been deleted.

Production: details of the RADIONUCLIDE PRODUCTION and RADIOCHEMICAL SYNTHESIS are transferred to the knowledge database in-line with current practice for monographs on PET preparations. It is prescribed that the radionuclide is derived from a gaseous target. The quality of chemical precursors is covered by the general monograph *Chemical precursors for radiopharmaceutical preparations (2902)*. The tests for L-homocysteine thiolactone hydrochloride have thus been deleted from this specific monograph.

Identification: approximate half-life has been included and the wording of the other identification tests has been harmonised across the ^{11}C-monographs.

RADIONUCLIDIC PURITY:

The established standard methods for production of carbon-11 use the $^{14}N(p,\alpha)^{11}C$ nuclear reaction by proton bombardment of a nitrogen/hydrogen or nitrogen/oxygen target gas mixture producing either [^{11}C]methane or [^{11}C]carbon dioxide respectively. With these methods no measurable amounts of long-lived radionuclide impurities are formed in the target material. Theoretically fluorine-18 in the form of [^{18}F]fluoride could be formed by the $^{18}O(p,n)^{18}F$ nuclear reaction on oxygen-18 in the target gas. However, no measurable amounts of fluorine-18 are formed due to the low concentration (0.2 per cent) of oxygen-18 in the trace amounts of oxygen in the target gas. Furthermore, any [^{18}F]fluoride ion formed is deposited on the target holder. Depending on the material in the foil separating the cyclotron from the target material long-lived metallic radionuclides could be formed, especially if Havar foils are used. However, these radionuclides are cationic metals and not transferred into the target gas. They are thus quantitatively retained in the foil. The primary carbon-11 precursors formed in the target gas, [^{11}C]methane or [^{11}C]carbon dioxide, are subjected to purification and further chemical transformation to radiopharmaceuticals before use. Considering the above there is no scientific rationale for the determination of individual radionuclidic impurities in carbon-11 radiopharmaceuticals and the test for radionuclidic purity is therefore solely an examination of the gamma-ray spectrum.

Radioactivity: the wording has been harmonised across all ^{11}C- and ^{15}O-monographs, also published in this issue of Pharmeuropa..

Labelling: the Labelling section has been removed because these details appear in the general monograph on *Radiopharmaceutical preparations (0125)*.

Raclopride ([^{11}C]methoxy) injection (1924)

It has been shown that determination of the radioactive half-life of ^{11}C- and ^{15}O-radiopharmaceutical preparations cannot be used as a test for radionuclidic purity with the required sensitivity. There is also no scientific rationale for the determination of individual radionuclidic impurities in preparations containing these radionuclides produced from a gaseous target. Determination of the approximate half-life does however contribute to the identification of the radionuclide.

In view of the above, the Identification and Radionuclidic purity sections have been revised. Other editorial changes have also been made for harmonisation purposes.

A FORMULA and the RELATIVE MOLECULAR MASS have been added.

Definition: The Content statement has been changed to that in The Guide for the Elaboration of Monographs on Radiopharmaceutical Preparations and the purity statements have been deleted.

Production: Details of the RADIONUCLIDE PRODUCTION and RADIOCHEMICAL SYNTHESIS are transferred to the knowledge database in line with current practice for monographs on PET preparations. It is prescribed that the radionuclide is derived from a gaseous target. The quality of chemical precursors is covered by the general monograph *Chemical precursors for radiopharmaceutical preparations (2902)*. The tests for (*S*)-3,5-Dichloro-2,6-dihydroxy-*N*-[(1-ethylpyrrolidin-2-yl)methyl]benzamide hydrobromide have thus been deleted from this specific monograph.

Identification: Approximate half-life has been included and the wording of the other identification tests has been harmonised across the ^{11}C-monographs.

RADIONUCLIDIC PURITY:

The established standard methods for production of carbon-11 use the $^{14}N(p,\alpha)^{11}C$ nuclear reaction by proton bombardment of a nitrogen/hydrogen or nitrogen/oxygen target gas mixture producing either [^{11}C]methane or [^{11}C]carbon dioxide respectively. With these methods no measurable amounts of long-lived radionuclide impurities are formed in the target material. Theoretically fluorine-18 in the form of [^{18}F]fluoride could be formed by the $^{18}O(p,n)^{18}F$ nuclear reaction on oxygen-18 in the target gas. However, no measurable amounts of fluorine-18 are formed due to the low concentration (0.2 per cent) of oxygen-18 in the trace amounts of oxygen in the target gas. Furthermore, any [^{18}F]fluoride ion formed is deposited on the target holder. Depending on the material in the foil separating the cyclotron from the target material long-lived metallic radionuclides could be formed, especially if Havar foils are used. However, these radionuclides are cationic metals and not transferred into the target gas. They are thus quantitatively retained in the foil. The primary carbon-11 precursors formed in the target gas, [^{11}C]methane or [^{11}C]carbon dioxide, are subjected to purification and further chemical transformation to radiopharmaceuticals before use. Considering the above there is no scientific rationale for the determination of individual radionuclidic impurities in carbon-11 radiopharmaceuticals and the test for radionuclidic purity is therefore solely an examination of the gamma-ray spectrum.

Radioactivity: The wording has been harmonised across all ^{11}C- and ^{15}O-monographs, also published in Pharmeuropa 32.4.

Labelling: The Labelling section has been removed because these details appear in the general monograph on *Radiopharmaceutical preparations (0125)*.

Sodium acetate ([1-^{11}C]) injection (1920)

It has been shown that determination of the radioactive half-life of ^{11}C- and ^{15}O-radiopharmaceutical preparations cannot be used as a test for radionuclidic purity with the required sensitivity. There is also no scientific rationale for the determination of individual radionuclidic impurities in preparations containing these radionuclides produced from a gaseous target. Determination of the approximate half-life does however contribute to the identification of the radionuclide.

In view of the above, the Identification and Radionuclidic purity sections have been revised. Other editorial changes have also been made for harmonisation purposes.

The RELATIVE MOLECULAR MASS has been added.

Definition: The Content statement has been changed to that in The Guide for the Elaboration of Monographs on Radiopharmaceutical Preparations.

Production: Details of the RADIONUCLIDE PRODUCTION and RADIOCHEMICAL SYNTHESIS are transferred to the knowledge database in-line with current practice for monographs on PET preparations. It is prescribed that the radionuclide is derived from a gaseous target. The quality of chemical precursors is covered by the general monograph *Chemical precursors for radiopharmaceutical preparations (2902)*. The test for methylmagnesium bromide has thus been deleted from this specific monograph.

Identification. Half-life determination replaced by approximate half-life determination, due to short half-life. The former limit of 19.9 min to 20.9 min corresponded to a range of - 2.3 per cent to + 2.7 per cent. The new limit is 18.3 min to 22.4 min and corresponds to a tolerance of ± 10 per cent. The intention was to rationalise and harmonise the ‘approximate half-lives’

values in all these ^{11}C- and ^{15}O-monographs to a tolerance of ± 10 per cent. The wording of the other identification tests has been harmonised across the ^{11}C-monographs.

RADIONUCLIDIC PURITY:

The established standard methods for production of carbon-11 use the $^{14}N(p,\alpha)^{11}C$ nuclear reaction by proton bombardment of a nitrogen/hydrogen or nitrogen/oxygen target gas mixture producing either [^{11}C]methane or [^{11}C]carbon dioxide respectively. With these methods no measurable amounts of long-lived radionuclide impurities are formed in the target material. Theoretically fluorine-18 in the form of [^{18}F]fluoride could be formed by the $^{18}O(p,n)^{18}F$ nuclear reaction on oxygen-18 in the target gas. However, no measurable amounts of fluorine-18 are formed due to the low concentration (0.2 per cent) of oxygen-18 in the trace amounts of oxygen in the target gas. Furthermore, any [^{18}F]fluoride ion formed is deposited on the target holder. Depending on the material in the foil separating the cyclotron from the target material long-lived metallic radionuclides could be formed, especially if Havar foils are used. However, these radionuclides are cationic metals and not transferred into the target gas. They are thus quantitatively retained in the foil. The primary carbon-11 precursors formed in the target gas, [^{11}C]methane or [^{11}C]carbon dioxide, are subjected to purification and further chemical transformation to radiopharmaceuticals before use. Considering the above there is no scientific rationale for the determination of individual radionuclidic impurities in carbon-11 radiopharmaceuticals and the test for radionuclidic purity is therefore solely an examination of the gamma-ray spectrum.

Radioactivity: The wording has been harmonised across all ^{11}C- and ^{15}O-monographs, also published in this issue of Pharmeuropa.

Labelling: The Labelling section has been removed because these details appear in the general monograph on *Radiopharmaceutical preparations (0125)*.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Coriander oil (1820)

Chiral purity: *borneol R* reagent replaced by *(-)-borneol R* reagent to allow an unequivocal evaluation of the system suitability.

Lavender oil (1338)

Chiral purity: *borneol R* reagent replaced by *(-)-borneol R* reagent to allow an unequivocal evaluation of the system suitability

Rhubarb (0291)

Identification:

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

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

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

Anthraquinones: test for the determination of aloe-emodin, rhein, emodin, chrysophanol and physcion introduced.

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

MONOGRAPHS

Amylmetacresol (2405)

Identification: preparation deleted from IR test.

Related substances: status of impurity K changed from specified to unspecified, and the corresponding CRS strategy for *amylmetacresol for peak identification CRS* adapted accordingly; in preparation of reference solutions (a) and (b), volume expressed using fewer significant figures due to the qualitative use of these solutions.

Impurities: impurity K deleted from the transparency list since it is not a specified impurity any longer and its identity is unknown.

Benzydamine hydrochloride (2759)

Production: section deleted since impurity G is now covered in the TESTS section.

Impurity G: new LC-MS method introduced.

Cefalotin sodium (0987)

Characters: the solubility in anhydrous ethanol has been revised based on experimental data.

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

Colistimethate sodium (0319)

Composition and Related substances: in accordance with the definition given in the general chapter *2.2.46* for the normalisation procedure, the level of 0.05 per cent previously described as integration level has been renamed as disregard limit, under which peaks have to be excluded from the total area. In parallel, the description of the threshold of 0.50 per cent above which peaks have to be taken into account for the calculation of CMS and impurity contents, previously described as disregard limit, has been reworded and included in the description of the limits concerned.

In addition, the preparation of reference solution (d) has been amended and the reagent used to describe the column stationary phase has been modified.

Colistin sulfate (0320)

Composition and Related substances: the preparation of reference solution (b), used to calculate the signal-to-noise ratio, has been amended to align its concentration of polymyxin E1 with the disregard limit.

Crotamiton (1194)

Related substances: test updated. New column described to improve separation; several impurities added to the list, including specified impurity B.

Dexpanthenol (0761)

Related substances: an additional reference solution (d) containing dexpanthenol and impurities B and C (at about 0.5% relative to the test solution) is introduced for testing the resolution; reference solution (c), which is now only used to quantify impurities B and C, is updated accordingly.

Diclazuril for veterinary use (1718)

Identification: reference spectrum replaced by reference substance.

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

Enoxolone (1511)

Related substances: updated.

Calculation of percentage contents: quantitative determination of impurities.

Impurities: specifications and list of impurities revised based on recent data.

Erythromycin lactobionate (1098)

Related substances: based on batch data, impurity H, previously qualified as other detectable impurity, has been specified to a limit of maximum 1.0 per cent.

Impurities: the status of impurity H has been updated.

Estriol (1203)

Identification: 2nd identification series introduced.

Characters: solubility in a lipophilic solvent added.

Related substances and assay: modification of the preparation of the mobile phase to allow the control of artefacts.

Etanercept (2895)

Definition (Potency): to reflect the application of the corresponding International Units (IU) and the use of the Etanercept Biological Reference Preparation (BRP), the numeric range for potency (expressed in activity units per mass of protein) has been adjusted.

Assay (Potency): the monograph has been revised to include a cross-reference to the new general chapter on Cell-based assays for potency determination of TNF-alpha antagonists (*2.7.26*).

The detailed method instructions for the U937 apoptosis assay, given as an example procedure, have been deleted. A reference to “Procedure A” (U937 Apoptosis assay) described in the chapter *2.7.26* has been included instead of the procedure itself, while

maintaining the flexibility of the monograph; specific instructions for the preparation of the test and reference solutions have been kept and adapted accordingly.

A reference has been added to three other assay procedures that were also found to be suitable: the WEHI-164 cytotoxicity assay, the NF-κB-inducible reporter gene assay and the L929 cytotoxicity assay (Procedures B, C and D in the new chapter *2.7.26*). Specific instructions for the preparation of the test and reference solutions have been included.

Everolimus (2918)

Impurity A: the requirement for use of plastic labware has been deleted as it was shown that this precaution was not necessary and that other labware (e.g. glass) could be used. The wording concerning quantification of impurity A has been clarified.

Related substances: the limits for impurities E, F, H and J have been lowered to maximum 0.15 per cent ("unspecified impurities") in agreement with current batch data, and the new CRS for system suitability has been introduced. The wording concerning quantification of impurities has been clarified.

Felodipine (1013)

Related substances: quantitative expression of acceptance criteria described; individual limits added for impurities B and C.

Fructose (0188)

Identification A: modified in order to avoid the use of *ethylene chloride R* (REACH).

Glucose (0177)

Second Identification:

- test C modified in order to avoid the use of *ethylene chloride R* (REACH);

- current test D replaced by a colorimetric test based on Seliwanoff's reaction able to discriminate aldose (e.g. glucose) and ketose (e.g. fructose) sugars.

Glucose monohydrate (0178)

Second Identification:

- test C modified in order to avoid the use of *ethylene chloride R* (REACH).

- current test D replaced by a colorimetric test based on Seliwanoff's reaction able to discriminate aldose (e.g. glucose) and ketose (e.g. fructose) sugars.

Infliximab concentrated solution (2928)

Assay (Potency): the monograph has been revised to include a cross-reference to the new general chapter on *Cell-based assays for potency determination of TNF-alpha antagonists (2.7.26)*.

The detailed method instructions for the WEHI-164 cytotoxicity assay, given as an example procedure, have been deleted. A reference to "Procedure B" (WEHI-164 cytotoxicity assay) described in chapter *2.7.26* has been included instead of the procedure itself, while maintaining the flexibility of the monograph; specific instructions for the preparation of the test and reference solutions have been kept and adapted accordingly.

A reference has been added to three other assay procedures that were also found to be suitable: the U937 apoptosis assay, the NF-κB-inducible reporter gene assay and the L929 cytotoxicity assay (Procedures A, C and D in the new chapter *2.7.26*). Specific instructions for the preparation of the test and reference solutions have been included.

Isoniazid (0146)

Solubility: solubility in heptane added.

Impurity E: acetonitrile replaced by methanol in the preparation of solution A in order to avoid the degradation of isoniazid into impurity E in the test solution; system suitability test criterion referencing the area of the peak due to benzaldehyde azine.

Related substances: in preparation of reference solution (b), volume expressed using fewer significant figures due to the qualitative use of this solution; retention time of isoniazid and relative retention of impurity A updated.

Lactose (1061)

Second Identification: test B modified in order to avoid the use of *ethylene chloride R* (REACH); deletion of the SST in test B to reduce the cost for pharmacies and because the second identification as a whole is considered specific enough.

Lactose monohydrate (0187)

Second Identification: test B modified in order to avoid the use of *ethylene chloride R* (REACH); deletion of the SST in test B to reduce the cost for pharmacies and because the second identification as a whole is considered specific enough.

Levomepromazine hydrochloride (0505)

Definition: lower content limit tightened.

Characters: solubility in heptane added.

Identification: UV-Vis, TLC and melting point tests replaced by IR and Specific optical rotation tests. In the test for chlorides, *methanol R* replaces *water R* for both washing and suspending the precipitate.

Solution S: deleted as only used in one test.

Acidity or alkalinity: replaced by a pH test, based on the buffering properties of levomepromazine hydrochloride.

Related substances: TLC method replaced by LC, covering 5 new impurities.

Impurities: section added.

Mefloquine hydrochloride (1241)

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

Related substances: some changes made. More complete revision is ongoing.

Moxonidine (1758)

Assay: symmetry factor added as outside the range 0.8-1.8.

Octreotide (2414)

Related substances: symmetry factor was added as a system suitability criterion.

Ondansetron hydrochloride dihydrate (2016)

Assay: symmetry factor added as found to be outside the range 0.8-1.8.

Pivmecillinam hydrochloride (1359)

Related substances: due to the physical form of *pivmecillinam impurity C CRS*, the preparation of reference solution (c) has been adjusted. The grade of solvents has been amended in accordance with Technical Guide (2015).

Quinine hydrochloride dihydrate (0018)

Title: the degree of hydration has been added.

Identification: reaction (b) of chlorides deleted.

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

Raltegravir potassium (2887)

Related substances: based on recent laboratory results, correction factor deleted and limit updated accordingly; in the preparation of the solution for system suitability use of the substance to be examined instead of the CRS according to usual practice and volumes expressed using fewer significant figures due to the qualitative use of this solution.

Regorafenib tablets (3023)

Assay: the assigned content of *regorafenib monohydrate CR*S takes account of the water content; hence no conversion factor is needed for the calculation of the assay content of regorafenib tablets.

Rifaximin (2362)

Related substances: the one-step dissolution in the solvent mixture has been replaced by a two-step dissolution in acetonitrile and water to avoid solubility issues during the preparation of solutions. The reagent used to describe the stationary phase of the column has been modified.

Risedronate sodium 2.5-hydrate (2572)

Related substances B: impurity A no longer specified and no longer used for the quantification of impurities.

Sevoflurane (2269)

Related substances: replacement of ethylene chloride (class 2 solvent) by heptane (class 3 solvent).

Teriflunomide (3036)

Assay: increase of the symmetry factor based on recent experimental data.

Theophylline-ethylenediamine (0300)

Second identification:

- current tests A, C, F removed from the series;

- current test D replaced;

- TLC for identification of the theophylline moiety and colour reaction for the identification of the ethylenediamine moiety added.

Letters identifying the tests renamed throughout the Identification section.

Related substances: reagent used to describe stationary phase modified; grade of acetonitrile in mobile phase amended in accordance with Technical Guide (2015); Identification of impurities section added.

Theophylline-ethylenediamine hydrate (0301)

Second identification:

- current tests A, C, F removed from the series;

- current test D replaced;

- TLC for identification of the theophylline moiety and colour reaction for the identification of the ethylenediamine moiety added.

Letters identifying the tests renamed throughout the Identification section.

Related substances: reagent used to describe stationary phase modified; grade of acetonitrile in mobile phase amended in accordance with Technical Guide (2015); Identification of impurities section added.

Tibolone (1739)

Content: limits reviewed to reflect the change of assay method.

Identification: reference spectrum replaced by reference substance.

Assay: titration replaced by LC assay.

Tilidine hydrochloride hemihydrate (1767)

Identification: use of reference spectrum added in IR test.

Water for injections (0169)

Deletion of tests for inorganic substances in the section on sterilised water for injections (SWFI).

This section previously included tests for Acidity or alkalinity, Chlorides, Nitrates, Sulfates, Aluminium, Ammonium, and Calcium and magnesium. It also described (and still describes) a Conductivity test, with specific acceptance criteria, depending on the size of the container.

Based on well-known chemical and physical properties of water, and ions in water, it is possible to determine the minimum conductivity that these inorganic impurities would produce when present at the highest allowable concentration for each of the species according to the chemical tests.

Consequently, if the sample passed the conductivity test, it would necessarily pass each of the original chemical tests. In view of the above, the chemical tests Acidity or alcalinity, Chlorides, Nitrates, Sulfates, Ammonium, and Calcium and magnesium have been deleted in favour of a single, instrument-based, quantitative test.

The test for Aluminium, however, has been maintained, since it is a requirement for SWFI used in the manufacture of dialysis solutions.