Comments concerning revised texts published in Supplement 10.7

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the March session and published in Supplement 10.7.

When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.7. The details given below complete this information, but are not necessarily exhaustive.

The following details can also be consulted in the Knowledge database under View history.

GENERAL CHAPTERS

1. General notices

The General Notices (Ph. Eur. chapter 1) have been revised to clarify a number of items for users, to review their structure and contents and to include a section on medicinal products containing chemically defined active substances.

The main changes are:

- inclusion of a table of contents;

- numbering of the sections and sub-sections;

- replacement of 'method' or 'test method' by 'analytical procedure' in line with ICH Q2(R1);

- terminology harmonised and clarified to avoid multiple terms for the same thing (finished product, pharmaceutical preparation, medicinal product); 'medicinal product' used systematically;

- terms 'period of validity' and 'period of use' replaced by 'shelf life' and 're-test period', which are the terms used in the ICH guidelines (see 1.1.2.1 Scope);

- Inclusion of a sub-section on Demonstration of suitability of monographs (1.1.2.3);

- Quantities (1.2.1): reference to new chapter 2.1.7. Balances for analytical purposes added and wording modified to fit with this chapter;

- Solutions (1.2.6): definitions added for 'freshly prepared solution' and 'immediately before use';

- General chapters (1.3): clarification of their legal status;

- Materials for containers and containers (1.3.1): more details given, in line with the recent restructuring of these chapters;

- Characters (1.5.1.7): reference to general chapter 5.11 added and the table on solubility removed; inclusion of the paragraph on polymorphism currently in II. Introduction to the Ph. Eur.;

- Identification (1.5.1.8): clarification of first and second identification series and alternative identifications;

- Tests and assays (1.5.1.9): Limits: clarification of rounding; Chiral substances: paragraph from II. Introduction to the Ph. Eur. included here; Equivalents: example given;

- Functionality-related characteristics of excipients (1.5.1.13): section originally published in the General Notices replaced by paragraph from II. Introduction to the Ph. Eur. as the wording was considered to be clearer;

- Monographs on herbal drugs (1.5.2): current paragraphs gathered under this new sub-section;

- Monographs on medicinal products containing chemically defined active substances (1.5.3): new sub-section added; paragraphs on related substances and impurities adapted from the Technical Guide for the elaboration of monographs on medicinal products containing chemically defined active substances (Edition 2020).

2.2.48. Raman spectroscopy

The general chapter has been updated in view of the latest developments. This general revision mainly includes: an update on the section on response-intensity scale; a new section on spectral resolution, using calcium carbonate and a description of procedures for the comparison of spectra.

2.2.66. Detection and measurement of radioactivity

Radionuclidic purity: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

5.1.3. Efficacy of antimicrobial preservation

Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

5.2.7. Evaluation of efficacy of veterinary vaccines and immunosera

Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the EU regulation.

5.4. Residual solvents

Alignment to the latest version of the ICH Guideline Q3C (R8):

- 2-Methyltetrahydrofuran is a new Class 3 solvent with a permitted daily exposure (PDE) of 50 mg/day;

- Cyclopentylmethyl ether is a new class 2 solvent with a PDE of 15 mg/day;

- Tertiary-butyl alcohol is a new class 2 solvent with a PDE of 35 mg/day.

5.11. Characters section in monographs

Solubility: table and additional information currently included in the General Notices moved to this general chapter.

5.19. Extemporaneous preparation of radiopharmaceuticals

3-11 LABELLING. Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 3 new monographs published in Supplement 10.7.

GENERAL MONOGRAPHS

Essential oils (2098)

The general monograph has undergone almost complete revision. The chromatographic profile will be revisited in a subsequent revision.

Immunosera for veterinary use (0030)

Antimicrobial preservatives: terminology reviewed to replace “period of validity” by “shelf life” and “period of use after reconstitution / broaching” by “shelf life after reconstitution / broaching” which are the terms used in the ICH guidelines.

Products of fermentation (1468)

Identification, tests and assay: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Radiopharmaceutical preparations (0125)

Period of validity: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Vaccines for human use (0153)

Terminology reviewed to replace “period of validity” by “shelf life” and “period of use after broaching” by “shelf life after broaching” which are the terms used in the ICH guidelines.

Vaccines for veterinary use (0062)

2-2-1-1. Potency and immunogenicity and 2-2-3 Stability: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

2-2-2 Antimicrobial preservatives: Terminology reviewed to replace “period of validity” by “shelf life” and “period of use after reconstitution / broaching” by “shelf life after reconstitution / broaching” which are the terms used in the ICH guidelines.

DOSAGE FORMS

Liquid preparations for cutaneous application (0927)

The following tests have been added:

- Uniformity of delivered dose, for metered-dose liquid preparations intended for a systemic effect: inter-container test (Production) and intra-container test (Tests);

- Number of deliveries per container, for metered-dose preparations;

- Uniformity of dosage units, for preparations supplied in single-dose containers and intended for a systemic effect.

A definition for cutaneous foams has been included.

VACCINES FOR HUMAN USE

Anthrax vaccine for human use (adsorbed, prepared from culture filtrates) (2188)

Production: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

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

Production: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Haemophilus type b conjugate vaccine (1219)

Production: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Influenza vaccine (live, nasal) (2772)

Final lot: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Measles, mumps and rubella vaccine (live) (1057)

Final lot: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Measles, mumps, rubella and varicella vaccine (live) (2442)

Final lot: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Measles vaccine (live) (0213)

Final lot: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Mumps vaccine (live) (0538)

Final lot: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Rotavirus vaccine (live, oral) (2417)

Final lot: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Rubella vaccine (live) (0162)

Final lot: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

Smallpox vaccine (live) (0164)

Final bulk vaccine: Terminology reviewed to replace “period of validity” by “shelf life” which is the term used in the ICH guidelines.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Lemon oil (0620)

Optical rotation: path length of the sample cell changed to allow use of standard equipment; limits adapted accordingly.

Mandarin oil (2355)

Optical rotation: path length of the sample cell changed to allow use of standard equipment; limits adapted accordingly.

Senna leaflet dry extract, standardised (1261)

Identification: TLC replaced by HPTLC in accordance with chapter *2.8.25*.

Assay: unspecific absorbance assay replaced by more specific LC assay; content limits adapted accordingly.

Sweet orange oil (1811)

Optical rotation: path length of the sample cell changed to allow use of standard equipment; limits adapted accordingly.

MONOGRAPHS

Alfacalcidol (1286)

Related substances: modification of the preparation of reference solution (d) following the replacement of *alfacalcidol for impurity B identification CRS* by *alfacalcidol impurity B CRS*.

Atorvastatin calcium (2191)

Title, graphic formula, molecular formula, definition and characters: updated since the monograph now covers anhydrous atorvastatin calcium and several hydrates of the substance; lower content limit tightened.

Identification: former test C deleted; preparation of residue in test D added.

Enantiomeric purity: method optimised; limit updated.

Related substances: new LC method now covering 8 new impurities; limits updated.

Sodium: AAS method replaced by reference to Determination of elemental impurities (*2.4.20*), thus allowing any method covered by this general chapter.

Water: limits modified to take account of the different degrees of hydration now covered by the monograph.

Assay: method modified in line with the revision of the test for related substances.

Storage: section added.

Impurities: section updated.

Cefuroxime axetil (1300)

Related substances and impurities: the status of impurity E has been changed from specified impurity to other detectable impurity.

Chlortalidone (0546)

Related substances: gradient adjusted to allow a proper elution of impurity G.

Cyanocobalamin (0547)

Test for related substances: Replacement of the resolution by a peak-to-valley ratio as a system suitability criterion.

Deferasirox (2933)

As Deferasirox is a chelating agent and amber or dark glass contains iron that leaches out of the glass, the glassware should be clear and low actinic. Corresponding statement has been introduced in line with what is mentioned in the monograph *Deferasirox dispersible tablets (2934)*.

Etomidate (1514)

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market.

Flucloxacillin sodium monohydrate (0668)

Title: the degree of hydration has been added.

Production: as some manufacturers may not use *N*,*N*-dimethylaniline in their production process, the control of this impurity has been moved from the Tests section to the Production section. Consequently, the requirement to evaluate the potential presence of *N*,*N*-dimethylaniline and to validate the production method to demonstrate that it is not detectable above the limit of 20 ppm has been introduced.

Characters: the solubility in dichloromethane has been added.

Specific optical rotation: the test has been removed as the quality is adequately controlled with the improved method for related substances.

Related substances: an improved LC method has been introduced with limits based on the quality of the substance used in the manufacturing of currently approved products.

N,N-dimethylaniline: the test has been removed and the control of this impurity is addressed under the new Production section.

Assay: a revised method has been introduced based on the improved LC method used for related substances.

Impurities: additional impurities have been included and structures modified based on currently available data.

Formoterol fumarate dihydrate (1724)

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; system suitability criterion amended.

Gonadorelin acetate (0827)

Related substances: the incorrect indication of impurity D co-eluting with impurity C was amended and impurity D was reclassified as unspecified impurity in accordance with current batch data. Consequently, the system suitability criterion was adjusted to calculate the resolution between peaks due to impurities C and E.

Human anti-D immunoglobulin (0557)

Potency: Method A (agglutination-based method) requires specialised equipment (AutoAnalyser), which has increasingly become less available in manufacturers' and national laboratories. The monograph has been revised to reflect current practices for determination of potency of human anti-D immunoglobulin and to address the challenges of Method A phasing out. In light of scientific data, method A (AutoAnalyser), method B (competitive enzyme-linked immunoassay) and method C (flow cytometry) are considered interchangeable.

Production: The structural integrity of the Fc part of anti-D antibodies plays an important role for product efficacy. In view of reported differences between Fc-stability indicating methodologies, a general requirement has been added outlining demonstration of integrity of the Fc part using a suitable method.

Human anti-D immunoglobulin for intravenous administration (1527)

Potency: Method A (agglutination-based method) requires specialised equipment (AutoAnalyser), which has increasingly become less available in manufacturers' and national

laboratories. The monograph has been revised to reflect current practices for determination of potency of human anti-D immunoglobulin and to address the challenges of Method A phasing out. In light of scientific data, method A (AutoAnalyser), method B (competitive enzyme-linked immunoassay) and method C (flow cytometry) are considered interchangeable.

Production. The structural integrity of the Fc part of anti-D antibodies plays an important role for product efficacy. In view of reported differences between Fc-stability indicating methodologies, a general requirement has been added outlining demonstration of integrity of the Fc part using a suitable method.

Hyaluronidase (0912)

The CAS number was deleted as the one previously given in the monograph, which only covers hyaluronidase obtained from mammalian testes, was widely associated with the enzyme also obtained from different sources.

Hypromellose phthalate (0347)

Chlorides: 5 min standing step, protected from light, added.

Labelling: black diamonds added to indicate that this is a non-harmonised attribute.

Indapamide (1108)

Wording of the limit test for impurity A revised.

Marbofloxacin for veterinary use (2233)

Related substances: reference solution (b) adapted to accommodate new CRS strategy.

Methylprednisolone (0561)

Second identification:

- TLC method revised to avoid the use of ether;

- intensity of fluorescence added in test D to allow discrimination of the substance from prednisolone.

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

Miconazole (0935)

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

Miconazole nitrate (0513)

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; system suitability criterion amended.

Oxytetracycline hydrochloride (0198)

Identification B: wording changed to refer to chromatograms obtained in assay.

Related substances: hydrochloric acid replaced by a mixture of acetonitrile and oxalic acid for the preparation of test and reference solutions in order to improve their stability. Peak-to-valley ratio given as system suitability requirement adjusted due to the change of solvent. Grades of solvent in mobile phase amended in accordance with Technical Guide (2015).

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

Paracetamol (0049)

Related substances: description of test solution and reference solution containing *paracetamol impurity J CRS* modified in order to ensure appropriate dissolution by dissolving the substances first in methanol; precolumn deleted; column length, diameter and particle size increased to lower back-pressure; refrigerated autosampler introduced to avoid degradation of impurity K; gradient, flow rate and injection volume also modified; new unspecified impurity covered (i.e. impurity O).

Impurities: section updated.

Prednisolone acetate (0734)

Second identification (test C): intensity of the fluorescence added to allow discrimination of the substance from methylprednisolone acetate.

Racecadotril (2171)

Related substances. Preparation of reference solution (b) modified.

Teicoplanin (2358)

Chemical structure: the structure of teicoplanin $A_{2\text{-}1a}$ component has been revised.

Terpin monohydrate (2940)

Related substances: *trans-terpin R* replaced by the corresponding CRS.

Tetracaine hydrochloride (0057)

Characters: solubility in heptane added; melting point statement simplified to a wider range; statement on polymorphism introduced.

Identification: need to avoid recrystallisation stressed in test A; test B deleted from first identification since IR is able to discriminate tetracaine hydrochloride from other local anesthetic APIs.

Related substances: in the preparation of the test solution, volume and mass are expressed using more significant figures due to the quantitative use of this solution; reagent used to describe stationary phase modified; grade of water used in mobile phase A amended in accordance with Technical Guide (2015); retention time and relative retentions updated; correction factor of impurity B modified; acceptance criteria expressed in quantitative style.

Assay: non-volumetric solution of hydrochloric acid now prescribed.

Thiopental sodium and sodium carbonate (0212)

Related substances: reference solution (b) adapted to accommodate new CRS strategy.

Trifluridine (2910)

Related substances: preparation of reference solution (c).