

Comments concerning revised texts published in Supplement 9.3

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November 2016 session and published in Supplement 9.3.

When a text has been technically revised, this is indicated by horizontal or vertical lines in the margin of the supplement. 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

2.1.6. Gas detector tubes

Modification of minimum value to be indicated on hydrogen sulfide detector tubes; addition of descriptions of arsine and phosphine detector tubes.

2.2.37. X-ray fluorescence spectrometry

This general chapter has undergone a general revision and has been completely rewritten in order to introduce modern equipment and the current applications of the XRF technique. Parameters for instrument performance have been added.

2.2.49. Falling ball and automatic rolling ball viscometer methods

General chapter revised to include automatic rolling ball viscometer description.

2.4.20. Determination of elemental impurities

Changes for alignment with the terminology of ICH Q3D guideline on elemental impurities.

2.6.14. Bacterial endotoxins

The general chapter has been revised to indicate that it has undergone pharmacopoeial harmonisation and to include the reference to chapter 5.8. *Pharmacopoeial harmonisation*.

2.6.16. Tests for extraneous agents in viral vaccines for human use

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, this general chapter has been revised to be harmonised with general chapter 5.2.3. *Cell substrates for the production of vaccines for human use*, and in light of the scientific arguments from the article 'Systematic evaluation of *in vitro* and *in vivo* adventitious virus assays for the detection of viral contamination of cell banks and biological products' by J. Gombold, S. Kavakasis et al. and R.L. Sheets., *Vaccine* 32 (24) (2014) p. 2916-2926. The general chapter has been completely

revised and rewritten for clarity; it is now based on descriptions of the tests to be performed instead of the different stages of production.

In summary, the major revisions concern:

- the introduction of a risk assessment to build the testing strategy, that must be based on a full package of suitable tests with reference to general chapter 5.1.7. *Viral safety*;
- recommendations on the tests to be performed at the different stages is now indicated in a table;
- tests on adult mice and guinea pigs deleted, as they are redundant due to the presence of other tests concerning risk mitigation;
- tests on suckling mice and control eggs are used if the risk assessment indicates that these tests provide risk mitigation when taking into account the overall testing package;
- for the test on suckling mice, the subinoculation step is deleted to cut down on the use of animals and to be in line with the recommendations of the J. Gombold article; the observation period is harmonised with that prescribed in WHO TRS 978 Annex 3 and general chapter 5.2.3;
- the test for mycobacteria includes introduction of nucleic acid amplification techniques and modification of the sample volume to be tested in order to align it with general chapter 2.6.2. *Mycobacteria* (also aligned with WHO TRS 978 for cell substrates) ;
- test for spiroplasmas revised in accordance with general chapter 5.2.3;
- test for extraneous agents in cell cultures revised to include introduction of permissive cell lines other than VERO and MRC5 (e.g. HeLa, MDCK, A549, BT, RK13, CHO, CEF) depending on the manufacturing process of the product, the source of the virus strain, the cell substrates and raw materials and the incubation temperature for the growth of particular viruses;
- introduction of molecular biology methods for specific extraneous agents;
- introduction of broad molecular methods (such as high throughput sequencing) for broad detection of all viruses;
- test for avian leucosis virus includes a more detailed assay and refers to general chapter 2.6.24. *Avian viral vaccines: tests for extraneous agents in seed lots*.

2.6.17. Test for anticomplementary activity of immunoglobulin

The name of the BRP *human immunoglobulin (ACA and molecular size) BRP* has been changed to *human immunoglobulin for anticomplementary activity BRP* in order to restrict its use to the test described in this chapter due to the difficulty in producing batches able to fully meet the requirement for both tests.

2.7.9. Test for Fc function of immunoglobulin

The name of the BRP *human immunoglobulin (Fc function and molecular size) BRP* has been changed to *human immunoglobulin for Fc function BRP* in order to restrict its use to the test described in this chapter due to the difficulty in producing batches able to fully meet the requirement for both tests.

5.2.3. Cell substrates for the production of vaccines for human use

Revision to harmonise with general chapter 2.6.16. *Extraneous agents in viral vaccines for human use*, which is revised in parallel.

Tests in animals: test in adult mice deleted and paragraph title updated to 'tests in suckling mice'; sentence added for introduction of a risk assessment to build the testing strategy.

Tests in eggs: sentence added for introduction of a risk assessment to build the testing strategy.

Tests for specific viruses: rewording of sentences regarding NAT and broad molecular methods to be in line with the wording used in general chapter 2.6.16.

The sentence regarding the assessment 'the capacity of the process to remove/inactivate specific virus must take into account the origin and culture history of the cell line' is a general sentence on how to proceed, it has been moved to the section Infectious extraneous agents.

Tests for viruses using broad molecular methods: the sentence regarding the investigation of 'the presence of infectious extraneous agents that has to be made where positive results are found by NAT or broad molecular methods' is a precision on how the test is to be completed, the sentence has been added to this section and deleted from the section Infectious extraneous agents.

Table 5.2.3.-1 has been amended accordingly.

5.8. Pharmacopoeial harmonisation

Information modified for several excipients and 1 general chapter (2.6.1), and added for 2 excipients and 1 general chapter (2.6.14).

5.20. Elemental impurities

This general chapter has been revised to replace the reference to the EMA guideline on the specification limits for residues of metal catalysts and metal reagents by the basic principles (introduction and scope) of the ICH Q3D guideline on elemental impurities. It also outlines the application of the guideline within the context of the European Pharmacopoeia.

The ICH Q3D guideline itself, together with the supportive modules developed by the ICH Q3D Implementation Working Group, is available on the ICH website, ensuring a consistent and complete source of information.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include a new monograph published in Supplement 9.3.

GENERAL MONOGRAPHS

Pharmaceutical preparations (2619)

Elemental impurities. Following adoption of the ICH Q3D guideline, a reference to general chapter 5.20 (that reproduces the principles of this guideline) has been introduced in this general monograph, making this guideline legally binding for pharmaceutical preparations falling within its scope.

Additionally, a sentence has been added to draw attention to the common regulatory approach (e.g. good manufacturing practices) that the manufacturer of the pharmaceutical preparation is responsible for the appropriate quality of its product, irrespective of whether the product falls within the scope of ICH Q3D or not. This is intended to avoid potential misinterpretation that may be induced by the deletion of some tests of elemental impurities in individual monographs on substances for pharmaceutical use.

Substances for pharmaceutical use (2034)

The ICH Q3D guideline represents a change of paradigm in the control of elemental impurities by defining permitted daily exposures for elemental impurities to be applied to medicinal products. As part of the Ph. Eur. implementation strategy, references to the heavy metals tests (2.4.8) have been deleted from individual monographs on substances for pharmaceutical use (except those for veterinary use only). Further implementation steps include a revision of this general monograph to clarify the expectations with regard to elemental impurities for substances for pharmaceutical use.

Production. Section updated accordingly, as only the manufacturer of a substance for pharmaceutical use knows which elemental impurities may be potentially introduced as catalysts and reagents, and whose levels would therefore need to be controlled. Control in this context should be understood as a comprehensive approach following the principles of risk management, which may include analytical testing if appropriate.

Elemental impurities. A new subsection has been added to explain the absence of tests in monographs on substances for pharmaceutical use unless otherwise prescribed.

DOSAGE FORMS

Capsules (0016)

Definition sections: aligned with Standard Terms.

Tests: wording clarified for dissolution test.

Modified-released capsules: Production section deleted as covered by dissolution test in general Tests section.

Gastro-resistant capsules: dissolution test deleted as already listed in general Tests section; Production section deleted as covered by dissolution test in general Tests section.

Cachets: Labelling section deleted.

Chewing gums, medicated (1239)

Dissolution: requirements moved from Production section to Tests section.

Intraruminal delivery systems (1228)

Title: 'intraruminal delivery systems' considered more suitable for this dosage form, the term 'devices' being linked to medical devices.

Tests: 'tablet' has been replaced by 'dosage unit'.

Liquid preparations for oral use (0672)

Tests: single-dose preparations that are emulsions should be tested for uniformity of content, not uniformity of mass; wording clarified for Dose and uniformity of dose of oral drops.

Definition (Powders and granules for oral solutions and suspensions, Powders for oral drops, Powders and granules for syrups): references to monographs *Oral powders (1165)* and *Granules (0499)* deleted, as no additional information provided.

Oromucosal preparations (1807)

Metered-dose oromucosal sprays and sublingual sprays: test for uniformity of dosage units deleted for suspensions and emulsions as uniformity of delivered dose considered more suitable and sufficient for these preparations.

Compressed lozenges, Sublingual tablets and buccal tablets, Mucoadhesive preparations, Orodispersible films: reference to general chapter 2.9.3 provided for dissolution test (harmonised with monographs *Capsules (0016)* and *Tablets (0478)*).

Tablets (0478)

Subdivision of tablets: break-marks must be functional; in cases where fractions of tablets are necessary to deliver the intended dose stated in the labelling, the efficacy of the break-mark is assessed with respect to uniformity of mass of the subdivided parts.

Tests: wording clarified for dissolution test.

Gastro-resistant tablets: dissolution test deleted as already listed in general Tests section; definition amended; Production section deleted as covered by dissolution test in general Tests section.

Tablets for use in the mouth: section deleted as it is within the scope of *Oromucosal preparations (1807)*.

Modified-release tablets: Production section deleted as covered by dissolution test in general Tests section.

Oral lyophilisates: definition amended.

Veterinary liquid preparations for cutaneous application (1808)

Teat dips, Teat sprays, Udder-washes: categories other than disinfectants might be used.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Pentetate sodium calcium for radiopharmaceutical preparations (2353)

Heavy metals (2.4.8): test deleted as the requirements for control of metal catalysts and metal reagent residues as outlined in the general monograph *Chemical Precursors for Radiopharmaceutical Preparations (2902)* are applicable.

Bacterial endotoxins (2.6.14): test deleted as the requirements for bacterial endotoxins outlined in the general monograph *Chemical Precursors for Radiopharmaceutical Preparations (2902)* are applicable.

Labelling: section removed as the requirements for labelling outlined in the general monograph *Chemical Precursors for Radiopharmaceutical Preparations (2902)* are applicable.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Angelica dahurica root (2556)

Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Angelica pubescens root (2557)

Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Barbary wolfberry fruit (2612)

Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Clematis arandii stem (2463)

Identification B: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Uncaria stem with hooks (2729)

Assay: instruction to use freshly prepared solutions and a cooled autosampler introduced.

MONOGRAPHS

Aceclofenac (1281)

Related substances: description of reference solution used to identify and quantify impurity I has been modified due to renaming of *diclofenac impurity A CRS* to *aceclofenac impurity I CRS*, as this external standard is no longer used in the monographs for diclofenac sodium or diclofenac potassium. The section 'identification of impurities' has been updated and improved.

Aluminium magnesium silicate (1388)

Definition: requirements for viscosity and ratio of aluminium content to magnesium content included for the different types.

Identification: X-ray identification included as an alternative to identification tests A, B and C, which have been improved.

Viscosity: test added.

Assay: methods for aluminium and magnesium revised.

Functionality-related characteristics (FRCs): section added.

Alverine citrate (2156)

Related substances: description of reference solution (c) amended.

Aspartic acid (0797)

Identification: TLC previously used in test for ninhydrin-positive substances now only used for Identification E.

Enantiomeric purity: test added as the D-enantiomer is a possible synthesis impurity that may be present.

Other dicarboxylic acids: LC introduced to cover dicarboxylic acids other than aspartic acid, which is not detected by the method.

Ninhydrin-positive substances, Ammonium: former methods replaced by LC using amino acid analyser.

Assay: potentiometric end-point determination introduced.

Azithromycin (1649)

Related substances: additional impurity (impurity Q) added to list of specified impurities; impurity Q co-elutes with impurities D and J and has been specified within sum of impurities D, J and Q.

Impurities: impurity Q included.

Betamethasone dipropionate (0809)

Related substances: new specified impurity controlled by current LC method introduced; system suitability criterion modified accordingly.

Ceftazidime pentahydrate (1405)

Related substances, Assay: as the CRS for peak identification is produced by lyophilisation, the corresponding reference solutions are now prepared by dissolving the contents of the CRS vial rather than by weighing.

Ceftazidime pentahydrate with sodium carbonate for injection (2344)

Related substances, Assay: as the CRS for peak identification is produced by lyophilisation, the corresponding reference solutions are now prepared by dissolving the contents of the CRS vial rather than by weighing.

Chlorhexidine diacetate (0657)

Related substances: description of reference solution (a) amended.

Chlorhexidine digluconate solution (0658)

Related substances: description of reference solution (a) amended.

Chlorhexidine dihydrochloride (0659)

Related substances: description of reference solution (a) amended.

Clindamycin hydrochloride (0582)

Content: lower limit increased to take account of limit for total impurities.

Characters: updated to state that substance is slightly hygroscopic.

Identification B: updated to clarify the use of the upper layer in the mobile phase preparation.

Related substances: description of stationary phase updated; resolution criteria for system suitability introduced; limit for 'any other impurity' lowered to 0.5 per cent based on batch data from manufacturers.

Impurities: structures of 3 additional impurities included.

Deferoxamine mesilate (0896)

Identification: 2nd identification series deleted.

pH: limits revised based on batch data.

Related substances test A: method revised for better control of related substances; limits updated.

Related substances test B: method introduced to cover deferoxamine mesilate produced by a synthetic process.

Bacterial endotoxins: monocyte-activation test (2.6.30) proposed as alternative to overcome inhibitory effect of deferoxamine mesilate on bacterial endotoxins test.

Assay: reference to calomel electrode deleted.

Impurities: section updated.

Gefitinib (2866)

Water: due to solubility issues, the sample is now introduced directly into the reaction cell.

Heparin calcium (0332)

Related substances: the previous text did not specify a quantitative limit for 'any other impurity' and compliance with the acceptance criterion depended on the sensitivity of the method; a disregard limit was therefore introduced, in line with the principles of general method 2.2.46. *Chromatographic separation techniques*.

Heparin sodium (0333)

Related substances: the previous text did not specify a quantitative limit for 'any other impurity' and compliance with the acceptance criterion depended on the sensitivity of the method; a disregard limit was therefore introduced, in line with the principles of general method 2.2.46. *Chromatographic separation techniques*.

Human coagulation factor IX (rDNA) concentrated solution (2522)

Impurities with molecular masses differing from that of human coagulation factor IX (rDNA): text updated to take account of the revised Ph. Eur. general chapter

2.2.31. *Electrophoresis*, which as of Supplement 8.7 includes a new section on gradient concentration gels for SDS-PAGE. As a consequence:

- the detailed composition of the 3 per cent and 15 per cent acrylamide solutions used to prepare the gradient gel (resolving gel) has been deleted;
- a detailed preparation of the stacking gel has been added.

Hydroxyethylcellulose (0336)

Definition: possibility of adding pH-stabilisers stated; limits for content added.

Identification: section split into 2 series; identification by IR added.

Glyoxal: title changed to Aldehydes since method not specific for control of glyoxal; result expressed as glyoxal.

Sulfated ash: stricter limit added for grades having a viscosity greater than 1000 mPa·s.

Assay: determination of molar substitution by GC with wide-bore capillary column.

Labelling: statement of any added pH-stabiliser included.

Functionality-related characteristics: cross-references added to test for viscosity and to assay.

Lactose (1061)

Information on the degree of harmonisation added.

Lactose monohydrate (0187)

Information on the degree of harmonisation added.

Lactulose (1230)

Related substances: volumes of solvents modified to obtain a 1:1 mixture of *water R* and *acetonitrile R* in reference solutions (a) and (c).

Magnesium aspartate dihydrate (1445)

Identification: TLC previously used in test for ninhydrin-positive substances now only used for Identification C.

Enantiomeric purity: test added as the *D*-enantiomer is a possible synthesis impurity that may be present.

Other dicarboxylic acids: LC introduced to cover dicarboxylic acids other than aspartic acid, which is not detected by the method.

Ninhydrin-positive substances, Ammonium: former methods replaced by LC using amino acid analyser.

Naloxone hydrochloride dihydrate (0729)

Related substances: reference solution (a) revised to reflect new preparation of *naloxone for peak identification CRS*.

Nortriptyline hydrochloride (0941)

Identification: substance not used in pharmacies for extemporaneous preparations, so 2nd identification deleted. Reaction (a) of test for chlorides modified to avoid the use of a reagent proscribed under the REACH regulation (potassium dichromate).

Related substances: description of stationary phase corrected.

Olive oil, refined (1456)

Identification: reference to the test for composition of fatty acids has been added since it is more specific than the identification of fatty oils by TLC; the latter has been maintained in the 2nd identification series.

Composition of fatty acids: 'and isomer' included in the limit for oleic acid.

Olive oil, virgin (0518)

Identification: reference to the test for composition of fatty acids has been added since it is more specific than the identification of fatty oils by TLC; the latter has been maintained in the 2nd identification series.

Composition of fatty acids: 'and isomer' included in the limit for oleic acid.

Prednisone (0354)

Content: upper limit updated to reflect change of assay method.

Identification: TLC test B replaced by cross-reference to LC for assay in 1st identification series; former TLC test C replaced by TLC test B in 2nd identification series.

Specific optical rotation: dioxan replaced by a less toxic solvent, ethanol (96 per cent) and limits revised accordingly.

Related substances: previous LC replaced by improved LC to control additional impurities; limits updated according to the current quality of products on the European market; limit for genotoxic impurity C set to 0.10 per cent based on ICH M7 guideline.

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

Impurities: section added.

Soya-bean oil, refined (1473)

Identification: reference to the test for composition of fatty acids has been added since it is more specific than the identification of fatty oils by TLC; the latter has been maintained in the 2nd identification series.

Composition of fatty acids: 'and isomer' included in the limit for oleic acid.

Storage, Labelling: sections updated.

Tiotropium bromide monohydrate (2420)

Related substances: limits updated based on new synthetic process and current batch data.

Impurities: section updated.

Tylosin for veterinary use (1273)

Definition: production restricted to certain strains of *Streptomyces fradiae*.

Characters: solubility updated based on current data.

Identification: tests B and C deleted as IR considered sufficient.

Appearance of solution: test introduced for control of parenteral applications.

Composition, Related substances: improved method capable of separating several impurities; limits for specified and total impurities introduced.

Loss on drying, Sulfated ash: limits reduced to reflect current market quality.

Impurities: section updated.

Tylosin phosphate bulk solution for veterinary use (1661)

Definition: production restricted to certain strains of *Streptomyces fradiae*; content revised to reflect current market quality.

Identification: previous tests A and B deleted and identification by IR introduced.

Composition, Related substances: improved method capable of separating several impurities; limits for specified and total impurities introduced.

Labelling: section removed.

Impurities: section updated.

Tylosin tartrate for veterinary use (1274)

Definition: production restricted to certain strains of *Streptomyces fradiae*; content revised to reflect current market quality.

Characters: solubility updated based on current data.

Identification: tylosin tartrate CRS introduced for IR spectrophotometry; previous test B deleted.

Appearance of solution: test introduced for control of parenteral applications.

Composition, Related substances: improved method capable of separating several impurities; limits for specified and total impurities introduced.

Storage: section updated.

Impurities: section updated.

Vindesine sulfate (1276)

Related substances: specifications updated based on recent batch data.

Acetonitrile: test deleted.

Water: test by thermogravimetry replaced by micro determination using the evaporation technique.

Storage: polypropylene replaced by polyethylene.

Vitamin A concentrate (oily form), synthetic (0219)

Assay (method B): preparation of reference solution (b) amended to allow for differences in the concentration of retinol acetate between batches of the CRS.

Vitamin A concentrate (powder form), synthetic (0218)

Assay: preparation of reference solution (b) amended to allow for differences in the concentration of retinol acetate between batches of the CRS.

Vitamin A concentrate (solubilisate/emulsion), synthetic (0220)

Assay: preparation of reference solution (b) amended to allow for differences in the concentration of retinol acetate between batches of the CRS.