Comments concerning revised texts published in Supplement 8.8

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the June 2015 session and published in Supplement 8.8.

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

2.2.3. Potentiometric determination of pH

The main changes concern the choice of buffers used for the calibration of the pH meter which is now more flexible and does not start obligatorily with an initial calibration at pH 4.0. Furthermore, the chapter now allows the use of commercially available, certified reference materials as buffer solutions.

2.2.46. Chromatographic separation techniques

Text modified to reflect current Ph. Eur. policy (system suitability, quantification).

2.4.22. Composition of fatty acids by gas chromatography

Quantitative analysis, Method A: the sentence “The content of oleic acid is the sum of oleic acid (18:1 n-9) and cis-vaccenic acid (18:1 n-7)” has been deleted.

2.4.32. Total cholesterol in oils rich in omega-3 acids

The chromatographic run time of the test and reference solutions has been reduced and the preparation of the test solution simplified. Accuracy is verified down to 0.2 mg/g of total cholesterol compared to 1.5 mg/g for the previous method. Ether is no longer used.

2.6.8. Pyrogens

The text has been revised to include a reference to general chapter 2.6.30. Monocyte-activation test as a potential replacement of the test for pyrogens, therefore avoiding the use of live animals. This revision is in line with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.
5.1.10. Guidelines for using the test for bacterial endotoxins

This general chapter has undergone a general revision with the following scope.

- In the context of the new bacterial endotoxins Ph. Eur. policy approved by the European Pharmacopoeia Commission at its 149th Session (June 2014), a section has been added (section 2-4) to include aspects to be considered when establishing an endotoxin limit for a specific substance or product; also, the text has been revised to reflect the fact that an endotoxin limit is not always provided in a specific monograph.

- Reference is made to general chapter 2.6.30. Monocyte-activation test as an alternative to the rabbit pyrogen test, and a recommendation is given to perform a risk assessment when using the bacterial endotoxin test as a pyrogenicity test, due to the potential for contamination by non-endotoxin pyrogens. In this respect, the previous section 11 concerning the replacement of the rabbit pyrogen test by a test for bacterial endotoxins has been substituted with a new text in agreement with a strategy to be applied for testing of bacterial endotoxins or non-endotoxin pyrogens. A distinction is made between replacement methods already described in the Ph. Eur. and other alternative methods.

- Reference is made to the use of alternative reagents to the Limulus amoebocyte lysate, such as recombinant factor C: this practice avoids the use of animal species and can be considered in the context of the use of an alternative method as described in the General Notices.

A number of additional specific points have been included in the revision.

- Method A is no longer declared as the reference method, and all methods A to F of general chapter 2.6.14. Bacterial endotoxins can be used. Where the method is stated in the monograph, the use of another method must be validated.

- The expression ‘threshold endotoxin concentration’ has been replaced by the more appropriate expression ‘endotoxin limit concentration’ to harmonise with general chapter 2.6.30. Monocyte-activation test.

- A new entry has been included in Table 5.1.10.-1 for formulations administered per square metre of body surface.

Finally, the structure of the general chapter has been modified to improve its clarity.

5.3. Statistical analysis of results of biological assays and tests

Equivalence testing: an explicit mention of ‘equivalence testing’ has been introduced in section 7.6. For further information, consult the Knowledge database.

5.4. Residual solvents

Alignment of the chapter to the latest version of the ICH Guideline Q3C(R5): the permitted daily exposure limit for cumene has been lowered to 0.7 mg/day (i.e. changed to a class 2 solvent).
GENERAL MONOGRAPHS

Radiopharmaceutical preparations (0125)

The general monograph Radiopharmaceutical preparations (0125) has been revised to exclude chemical precursors for radiopharmaceutical preparations from its scope following the creation of the general monograph Chemical precursors for radiopharmaceutical preparations (2902), which is published in the same supplement.

Substances for pharmaceutical use (2034)

The general monograph Substances for pharmaceutical use (2034) has been revised to exclude chemical precursors for radiopharmaceutical preparations from its scope following the creation of the general monograph Chemical precursors for radiopharmaceutical preparations (2902), which is published in the same supplement.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Dioscorea oppositifolia rhizome (2473)

Definition: updated as Dioscorea oppositifolia L. does not have internal or external bark, or fibre in its roots.

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

Ephedra herb (2451)

Definition: updated as herbal drug consists of whole or fragmented aerial part rather than the stem; mixture of 3 species now included as they can't be differentiated in the absence of reproductive organs.

Identification A: updated following revised definition.

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

Schisandra fruit (2428)

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

Assay: schisandrin R replaced by schisandrin CRS.
MONOGRAPHS

Alverine citrate (2156)

Characters: approximate melting point deleted.

Related substances: based on current batch data, limits updated and impurities A, B and E now listed as unspecified impurities; reference to rotary evaporator deleted as other equipment or procedures may be used.

Cetyl palmitate (1906)

Hydroxyl value: an instruction to perform the titration at a temperature between 55 °C and 70 °C in order to maintain the substance in a melted state has been introduced.

Dextromethorphan hydrobromide (0020)

Related substances: given the fact that the use of ammonium nitrate is either proscribed or restricted in several countries, it has been replaced by sodium nitrate.

Dimethylacetamide (1667)

Non-volatile matter: reference to rotary evaporator deleted as other equipment or procedures may be used.

Ergocalciferol (0082)

Definition: addition of antioxidant allowed; as in other vitamin D-related monographs, now stated that pre-ergocalciferol contributes to the activity.

Impurity B: TLC replaced by LC; title of the section changed.

Related substances: test added using LC.

Assay: current LC replaced by LC introduced for related substances; pre-ergocalciferol peak, if present, considered in calculation of content.

Impurities: section updated and 2 additional specified impurities added.

Ether (0650)

Storage: it is appropriate to store the substance at room temperature.

Ether, anaesthetic (0367)

Storage: it is appropriate to store the substance at room temperature.

Fenoterol hydrobromide (0901)

Identification: 2nd identification series deleted as identification test D contained a reagent proscribed under the REACH regulation (disodium tetraborate).

Related substances: as the correction factor for impurity A is 1.0, impurity A is now quantified using a dilution of the test solution rather than using the assigned content of impurity A in fenoterol hydrobromide CRS; the amount of CRS has been reduced.
Galactose (1215)

**Definition:** limits for content added.

**Identification B:** type of plate to be used added.

**Specific optical rotation:** deleted as test for related substances added.

**Proteins:** test added to control residual lactase used for production of galactose from lactose.

**Related substances:** LC test added.

**Assay:** section added using same LC method as test for related substances.

**Impurities:** section added.

Hard fat (0462)

**Identification:** identification tests B and C added to confirm the absence of additives in the substance.

**Unsaponifiable matter:** test deleted.

**Heavy metals:** test replaced by a test for nickel.

**Total ash:** test replaced by a test for sulfated ash.

**Functionality-related characteristics (FRCs):** section added.

Irbesartan (2465)

**Impurity B:** complete dissolution of the substance to be examined is essential for full recovery of impurity B. Irbesartan is practically insoluble in water and only sodium hydroxide solution is suitable as solvent. In order to run the test properly, a precolumn is necessary and has therefore been introduced along with a washing step.

Macrogolglycerol hydroxystearate (1083)

**Hydroxyl value:** based on current batch data, the limit range for the product containing 40 units of ethylene oxide per molecule has been widened to take account of different production methods used by different manufacturers.

Maltodextrin (1542)

**Identification B:** wording modified since colour change depends on hydrogen-donating substance.

Methacrylic acid - ethyl acrylate copolymer (1:1) (1128)

**Ethyl acrylate and methacrylic acid:** LC method improved and limit decreased based on current batch data.

Methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent (1129)

**Ethyl acrylate and methacrylic acid:** LC method improved and limit decreased based on current batch data.
Methacrylic acid - methyl methacrylate copolymer (1:1) (1127)

Identification A: comparison with reference spectrum replaced by comparison with CRS.

Methyl methacrylate and methacrylic acid: LC method improved and limits decreased based on current batch data.

Methacrylic acid - methyl methacrylate copolymer (1:2) (1130)

Identification A: comparison with reference spectrum replaced by comparison with CRS.

Methyl methacrylate and methacrylic acid: LC method improved and limits decreased based on current batch data.

Phenobarbital sodium (0630)

Content: limits enlarged to reflect change in assay method.

Characters: statement on polymorphism added.

Identification C: chloroform replaced by less-toxic solvent methylene chloride; amount of CRS reduced.

Related substances: TLC replaced by LC in accordance with current policy.

Assay: titration replaced by LC for related substances.

Impurities: section added.

Phenoxyethanol (0781)

Related substances: packed column replaced by capillary column; limit test replaced by quantitative determination.

Phenol: test deleted as phenol now controlled by GC for related substances.

Pyrantel embonate (1680)

Related substances: method revised to cover 2 new impurities; limits updated based on recent batch data; quantitative expression of acceptance criteria applied.

Sodium fluoride (0514)

Sulfates: the solution of boric acid proscribed under REACH regulation has been replaced by a solution of aluminium nitrate.

Sodium glycerophosphate, hydrated (1995)

Calcium: test for calcium added for substances used in the manufacture of parenteral preparations in order to prevent formation of a precipitate due to the presence of calcium at levels above 100 ppm.

Ubidecarenone (1578)

Content: limits updated to reflect change in assay method.

Related substances: in line with general monograph Substances for pharmaceutical use (2034), explicit acceptance criterion for unspecified impurities introduced; limits updated based on recent batch results.
**Water**: test introduced.

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

**Xylitol (1381)**

**Related substances**: reference to rotary evaporator deleted as other equipment or procedures may be used.

**Zopiclone (1060)**

**Related substances**: specifications updated based on recent batch data.