

Comments concerning revised texts published in Supplement 9.2

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the June 2016 session and published in Supplement 9.2.

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

2.2.1. Clarity and degree of opalescence of liquids

General revision to restructure the text and eliminate unnecessary repetition. The requirements for accuracy and repeatability of the instrument have been changed.

2.6.27. Microbiological examination of cell-based preparations

The revised chapter redefines the scope to exclude preparations covered by the EU Directives for human blood or blood components.

The approach to microbiological examination of cell-based preparations that was previously described in the general chapter took particular account of constraints linked to preparations of limited volume and restricted shelf-life. Provisions applicable to other types of cell-based preparations are now included:

- preparations for which the volume available for testing is not a limiting factor;
- preparations for which administration to the patient does not have to take place before results of the microbiological examination are available; and/or
- preparations whose production process makes them more prone to environmental contamination.

The main changes to the automated growth-based method include greater flexibility for the incubation temperature(s) and examples of temperature settings where the test volume allows 2 incubation conditions. In addition, in the list of micro-organisms used for method validation, *Yersinia enterocolitica* is replaced by *Micrococcus* sp., because it is more appropriate as an example of a common contaminant of cell-based preparations. Information about the sensitivity to be achieved during validation has also been included.

The revision has also been an opportunity to refer to general chapter 2.6.1. *Sterility*, which may be applied, and to introduce alternative rapid test methods, to be used with or without a pre-incubation step, by referring to general chapter 5.1.6. *Alternative methods for control of microbiological quality*.

An introduction has been added with a rationale for method selection according to the characteristics and constraints inherent to the cell-based preparation to be tested. The revised general chapter also includes considerations and recommendations concerning sampling, the sample composition, and 'negative-to-date' results.

2.6.30. Monocyte-activation test

As a result of a survey distributed by the EDQM in 2013 to users of the Ph.Eur., the following improvements have been made.

Introduction: the wording 'very steep dose-response curves' has been changed to 'very steep or non-linear dose-response curves' as the latter better characterises the responses when non-endotoxin contaminants are present.

Definitions: clarification added that calculation of the maximum valid dilution (MVD) is based on the endotoxin reference standard; the possibility of using an estimated limit of detection (LOD) based on historical data when calculating MVD has been introduced.

Cell sources and qualification

- Additional cross-references to sections relating to the qualification of cells according to their origin, preparation and/or intended use (i.e. for the detection of endotoxin and/or non-endotoxin contaminants) have been included in sections 5-1, 5-2, 5-4, 5-5 and 5-6.
- Section 5-4. Qualification of cells pooled from a number of donors: a caution statement has been added regarding the need to consider the averaging effect when cells are pooled.
- Section 5-5. Qualification of cryo-preserved cells: the repetitive description regarding the preparation of cell pools has been deleted.
- Section 5-6. Monocytic continuous cell lines: a statement regarding the limited use of monocytic cell lines for the detection of non-endotoxin pyrogens has been introduced.

Preparatory testing

- Section 6-1. Assurance criteria for the endotoxin standard curve: numerical example provided to illustrate the term 'as low as possible', which defines the blank.
- Section 6-2. Test for interfering factors: text revised so that the concentration of added endotoxin in the preparation or the diluent is to be justified and can be estimated before starting the test. In Method C, it is stated that the type of analysis used to compare the test and reference lots must be justified and validated for each preparation, that assay validity criteria are to be included and that the dilutions tested depend on the type of analysis used. In addition, more information is given on how to test preparations with an inherently high pyrogen content.
- Section 6-3. Method validation for non-endotoxin monocyte-activating contaminants: text revised to note that during preparatory testing, at least 2 non-endotoxin ligands for toll-like receptors must be used to validate the test system, 1 of which is also used to spike the test preparation, and that the choice of non-endotoxin pyrogens used should reflect the most likely contaminant(s) of the test preparation. In addition, more information is given regarding the available ligands that can be used.

Methods

- Section 7-1-1. Method A, Test procedure: regarding the qualification procedure applied to monocytes of different origin, the term 'qualified cells' has now been introduced throughout the text. Changes to Table 2.6.30.-1 have been made so that all 3 test solutions (A, B and C)

are to be spiked and not just the highest concentration. Solution D has therefore been deleted and replaced by solutions AS, BS and CS (i.e. spiked solutions A, B and C).

- Section 7-1-2. Calculation and interpretation: text reworded to reflect the changes in Table 2.6.30.-1. In addition, the text now states that dilutions with an invalid spike recovery are deleted from further analyses and that at least 1 valid dilution is required for a valid test.
- Section 7-1-3. Pass/fail criteria of the preparation: conditions for the use of monocytic cell lines have been deleted.
- Section 7-2-1/2. Method B, Table 2.6.30.-2: text updated accordingly, as above for Method A.
- Section 7-3. Method C. Reference lot comparison test: although there is flexibility on the type of analysis used, the analysis must be justified and validated for each product and is to include assay validity criteria; the text has been changed to reflect this. A statement has also been included to emphasise that the description of the test method includes just an example of a type of analysis which could be used.
- Section 7-3-2. Calculation and interpretation: numerical example provided to show a possible acceptance value.

Guidance notes

- Section 2-1. Information regarding the choice of methods: further clarification is given on the inappropriateness of Method A if the dose-response curve for the preparation to be examined is not parallel to that of the standard endotoxin curve. In addition, a notice has been added regarding the product specific validation and capacity of the chosen method to identify non-responders along with low and high responders to a particular product/contaminant(s) combination(s).
- Section 2-5. Cross-validation has been added. Regarding the presence of non-endotoxin pyrogens in the product, a recommendation to perform cross-validation of the monocyte-activation test together with the bacterial endotoxins test has been introduced. In the context of the 3Rs, the rabbit pyrogen test can be performed for cross-validation purposes where the monocyte-activation test cannot be validated.
- A new entry has been included in Table 2.6.30.-4 for 'Parenteral formulations administered per square metre of body surface', in accordance with the recently revised general chapter 5.1.10. Guidelines for using the test for bacterial endotoxins.
- It is now specified that MAT is considered as a replacement for the rabbit pyrogen test.

3.1.3. Polyolefins

Production: information about suitable types of silica introduced.

IR identification: absorption maxima deleted since the chapter covers a variety of materials which are further specified under chapters 3.1.4, 3.1.5, 3.1.6 and 3.1.7. Possibility of recording spectra directly on granules or hot pressed films introduced, since this is the technique most often used in current practice.

Solution S1: *water for injections R* replaced by *water R*.

Substances soluble in hexane: test deleted for technical reasons as it can be difficult to perform on certain materials due to the formation of gel which impairs the filtering step and therefore compromises the performance of the test.

Phenolic antioxidants: procedure C deleted; additives 11 and 12 are now determined using procedure B; quantitative expression of acceptance criteria introduced.

Non-phenolic antioxidants; Amides and stearates: TLC plate replaced.

3.1.4. Polyethylene without additives for containers for parenteral preparations and for ophthalmic preparations

IR identification: absorption maxima revised and tolerance added; possibility of recording spectra directly on granules or hot pressed films introduced, since this is the technique most often used in current practice.

Solution S1: water for injections R replaced by water R.

Substances soluble in hexane: test deleted for technical reasons as it can be difficult to perform on certain materials due to the formation of gel which impairs the filtering step and therefore compromises the performance of the test.

3.1.5. Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations

Production: information about suitable types of silica introduced.

IR identification: absorption maxima revised and tolerance added; possibility of recording spectra directly on granules or hot pressed films introduced, since this is the technique most often used in current practice.

Solution S1: water for injections R replaced by water R.

Substances soluble in hexane: test deleted for technical reasons as it can be difficult to perform on certain materials due to the formation of gel which impairs the filtering step and therefore compromises the performance of the test.

Phenolic antioxidants: procedure C deleted; additives 11 and 12 are now determined using procedure B; quantitative expression of acceptance criteria introduced.

Non-phenolic antioxidants; Amides and stearates: TLC plate replaced.

3.1.6. Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations

Production: information about suitable types of silica introduced.

IR identification: absorption maxima revised and tolerance added; possibility of recording spectra directly on granules or hot pressed films introduced, since this is the technique most often used in current practice.

Solution S1: water for injections R replaced by water R.

Substances soluble in hexane: test deleted for technical reasons as it can be difficult to perform on certain materials due to the formation of gel which impairs the filtering step and therefore compromises the performance of the test.

Phenolic antioxidants: procedure C deleted; additives 11 and 12 are now determined using procedure B; quantitative expression of acceptance criteria introduced.

Non-phenolic antioxidants; Amides and stearates: TLC plate replaced.

3.1.7. Poly(ethylene - vinyl acetate) for containers and tubing for total parenteral nutrition preparations

IR identification: absorption maxima revised and tolerance added; possibility of recording spectra directly on granules or hot pressed films introduced, since this is the technique most often used in current practice.

Solution S2: water for injections R replaced by water R.

Amides and stearates: concentration of reference solutions (b) and (c) corrected for consistency with limits set in the Production section; TLC plate replaced.

Substances soluble in hexane: test deleted for technical reasons as it can be difficult to perform on certain materials due to the formation of gel which impairs the filtering step and therefore compromises the performance of the test.

5.1.1. Methods of preparation of sterile products

This text has undergone a general revision and has been completely rewritten. The sections on the different sterilisation processes, where appropriate, now have the same format: principle, equipment, sterilisation cycle, cycle effectiveness and routine control; where required, specific information has been added.

Sterility assurance level: the reference to exponential inactivation has been removed as membrane filtration is not a first-order process.

Steam sterilisation: modern concepts for validation have been added.

Dry heat sterilisation: a wider description of the suitable equipment has been provided.

Ionising radiation sterilisation: the reference to European Notes for Guidance has been removed.

Gas sterilisation: 2 types of agents are defined: alkylating agents and oxidising agents; the establishment of the cycle effectiveness has been described in more detail.

Membrane filtration: the description of the microbial challenge test has been moved to general chapter 5.1.2. *Biological indicators and related microbial preparations used in the manufacture of sterile products*, published in the same supplement.

Aseptic assembly: freeze-drying under aseptic conditions is added.

5.1.2. Biological indicators and related microbial preparations used in the manufacture of sterile products

The general chapter has undergone significant revision as listed below.

Title: it has been adapted to take into account microbial preparations used for sterilisation grade filtration.

Introduction: describes when biological indicators (BIs) are intended to be used and what is outside the scope of the general chapter, including that BIs are in most cases only to be used for development of the sterilisation process and are not to be employed for routine monitoring unless otherwise stated in this general chapter. A definition of BIs is given and the processes in which they can be used are described. Importantly, the Introduction section introduces the concept of the use of reduced sterilisation process conditions in order to ensure the validity of the sterilisation process. It is also made clear that there should be no surviving micro-organisms when the biological indicator is subject to a full sterilisation process.

BIs for sterilisation processes: this section gives guidance on how BIs are selected and how they are used to characterise sterilisation processes.

A description is provided of 4 types of BIs for sterilisation processes: inoculated carriers, self-contained BIs, characterised spore suspensions and custom-made BIs.

Information regarding the quality requirements for BIs and user requirement specifications have been introduced.

BIs for heat sterilisation: the parameters of BIs for heat sterilisation are described and how a validation cycle is established. Further information on biological validation with reduced sterilisation cycles has been included.

BIs for moist heat sterilisation: it is recognised that *Geobacillus stearothermophilus* may not be suitable for sterilisation processes delivering an F_0 between 8 and 15, therefore a different test micro-organism may be used.

BIs for dry heat sterilisation: description of the reference conditions and an example of how survivor rates of typical BIs are affected by temperature variations are given.

BIs for gas sterilisation: this section sets out that the use of gas sterilisation for disinfection is outside the scope of the general chapter. There are a number of different types of gas sterilisation processes and no reference cycles, therefore no criteria to which the BIs shall comply have been defined. Suitable micro-organisms for ethylene oxide sterilisation are given. It is, however, the responsibility of the user to define the cycle and the suitability of any BI used.

BIs for ionising radiation sterilisation: it is recognised that BIs are not considered to be necessary for defining the suitability of the radiation sterilising dose, but their use may be required for the development and validation of ionising radiation sterilisation in specific cases. Information on test micro-organisms is given.

Microbial preparations for sterilisation grade filtration: information on test micro-organisms is now given for the validation of retention of micro-organisms using a membrane.

Indicators for depyrogenation processes: this section has been removed from this general chapter and will be published elsewhere in the Ph. Eur.

The following article was published in Pharmeuropa Bio & Scientific Notes and can be consulted on <http://pharmeuropa.edqm.eu/PharmeuropaBioSN/> (registration required) for further information:

K. Haberer, H. van Doorne. Biological indicators, tools to verify the effect of sterilisation processes - position paper prepared on behalf of Group 1 (biological methods and statistical analysis). *Pharmeur Bio Sci Notes* 2011(2):26-39.

5.1.6. Alternative methods for control of microbiological quality

The chapter has been completely revised and rewritten to take account of technological developments in alternative microbiological methods.

The introduction and the sections concerning the 3 major types of determinations specific to microbiological tests have been reworded and expanded. In addition, information on the use of alternative methods for process analytical technology (PAT) has also been given.

Under Identification tests, addition of:

- paragraph dealing with databases and their validation;
- some requirements on micro-organism culture for identification purposes;
- remark on a potential disadvantage of traditional biochemical and phenotypic techniques versus genotypic methods.

Under General principles of alternative methods:

- some methods have been removed, namely microcalorimetry and phage-based methods, and the former section on media development has been replaced by a section on growth detection using selective and/or indicative media;
- in the section on direct measurement, a new autofluorescence method has been added;
- the section on biochemical assays based on physiological reactions (2-3-1-5) has been expanded to include alternatives to the traditional Gram staining method;
- the section on genotypic techniques (2-3-2) has been extensively revised to reflect improvements in this field, including current DNA or RNA-based detection methods; there has also been revision of the critical aspects and potential uses to make them more relevant for users.

The section on validation of alternative microbiological methods has been restructured and now gives details of the validation process (both primary validation (3-2-3) and validation for the intended use (3-2-4)) as well as details on the validation of the different types of microbiological tests (3-3). As microbiological tests have 3 basic applications (qualitative, quantitative and identification), 3 separate sets of validation criteria are now included.

The validation example section has been removed from the chapter and will be added to the knowledge database at a later date. This will allow for the examples to evolve in a more flexible way and eliminate any misinterpretation of the purpose of the examples.

5.8. Pharmacopoeial harmonisation

Information modified for several excipients.

5.15. Functionality-related characteristics of excipients

Chapter completely reviewed and numerous modifications introduced to align better with ICH guideline *Q8 Pharmaceutical Development*.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include a new monograph published in Supplement 9.2.

GENERAL MONOGRAPHS

Herbal drugs (1433)

Definition: section slightly modified to take account of the fact that algae, fungi and lichen do not belong to the plant kingdom.

Dried herbal drugs: when used for the production of essential oils, an exemption has been introduced to evaluate on a case-by-case basis if a particular test needs to be performed or not.

Fresh herbal drugs: new section introduced as not all tests required for dried herbal drugs are considered equally suitable for fresh herbal drugs.

DOSAGE FORMS

Glossary (1502)

Basis: the definition has been reworded, including the notion of single-phase and multiphase systems.

Dispersion: the terms 'Colloidal dispersion', 'Emulsion' and 'Suspension' have been placed under the new entry 'Dispersion' with revised definitions.

Solution: some additional information on the state of the dissolved substances has been included.

Standard term: a more detailed definition has been elaborated.

VACCINES FOR VETERINARY USE

Furunculosis vaccine (inactivated, oil-adjuvanted, injectable) for salmonids (1521)

Batch potency test (section 2-3-1) : revised to clarify that alternative methods are not limited to serological methods.

Vibriosis (cold-water) vaccine (inactivated) for salmonids (1580)

Batch potency test (section 2-3-1) : revised to clarify that alternative methods are not limited to serological methods.

Vibriosis vaccine (inactivated) for salmonids (1581)

Batch potency test (section 2-3-1) : revised to clarify that alternative methods are not limited to serological methods.

Yersiniosis vaccine (inactivated) for salmonids (1950)

Batch potency test (section 2-3-1) : revised to clarify that alternative methods are not limited to serological methods.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Copper tetramibi tetrafluoroborate for radiopharmaceutical preparations (2547)

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

Iobenguane sulfate for radiopharmaceutical preparations (2351)

Identification test A: the use of an *iobenguane sulfate CRS* has been introduced replacing the reference spectra.

The test for bacterial endotoxins (2.6.14) and the labelling section have been deleted from the monograph. The requirements for bacterial endotoxins (2.6.14) and labelling as outlined in the general monograph *Chemical Precursors for Radiopharmaceutical Preparations (2902)* are applicable.

Medronic acid for radiopharmaceutical preparations (2350)

The test for bacterial endotoxins (2.6.14) and the labelling section have been deleted from the monograph. The requirements for bacterial endotoxins (2.6.14) and labelling as outlined in the general monograph *Chemical Precursors for Radiopharmaceutical Preparations (2902)* are applicable.

Sodium iodohippurate dihydrate for radiopharmaceutical preparations (2352)

The test for bacterial endotoxins (2.6.14) and the labelling section have been deleted from the monograph. The requirements for bacterial endotoxins (2.6.14) and labelling as outlined in the general monograph *Chemical Precursors for Radiopharmaceutical Preparations (2902)* are applicable.

Technetium (^{99m}Tc) biccisate injection (2123)

Radiochemical purity: inclusion of a further group of impurities determined by the TLC test. Limit for the sum of all impurities widened.

Technetium (^{99m}Tc) mebrofenin injection (2393)

Impurity A: modification of the preparation of reference solution (b) to achieve full dissolution of the CRS.

Tetra-O-acetyl-mannose triflate for radiopharmaceutical preparations (2294)

The test for bacterial endotoxins (2.6.14) and the labelling section have been deleted from the monograph. The requirements for bacterial endotoxins (2.6.14) and labelling as outlined in the general monograph *Chemical Precursors for Radiopharmaceutical Preparations (2902)* are applicable.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Acanthopanax bark (2432)

Definition: currently accepted botanical name introduced.

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

Aniseed (0262)

Water: limit for water content increased.

Astragalus mongholicus root (2435)

Definition: currently accepted botanical name introduced.

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

Assay: extraction procedure modified to improve efficiency (soxhlet extraction replaced by sonication, and solid phase extraction step deleted).

Aucklandia root (1797)

Identification: more detailed description provided for Identification A; illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

Coix seed (2454)

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

Drynaria rhizome (2563)

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

Eclipta herb (2564)

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

Eucommia bark (2412)

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

Myrrh (1349)

Commiphora mukul: TLC replaced by HPTLC allowing distinction between different resins.

Matter insoluble in ethanol: limit increased based on batch data.

Myrrh tincture (1877)

Identification: TLC replaced by same HPTLC used for *Myrrh (1349)*, allowing distinction between different resins.

Peppermint leaf (0406)

Identification C: TLC replaced by HPTLC to allow differentiation between different *Mentha* species.

Peppermint leaf dry extract (2382)

Identification: HPTLC method updated to allow differentiation between different *Mentha* species.

MONOGRAPHS

Amiloride hydrochloride dihydrate (0651)

Related substances: impurity C is now a specified impurity; the limit for total impurities has been increased accordingly.

Benzympenicillin potassium (0113)

Definition: means of production amended and lower content limit adjusted based on revised limits for total impurities.

Characters: appearance and solubility updated.

Identification: TLC test updated in line with current Style guide.

Appearance of solution: test introduced as substance can be for parenteral use.

Specific optical rotation, Absorbance: tests removed as deemed no longer required based on improved LC for related substances.

Related substances: improved LC introduced allowing for identification of 2 additional impurities; impurity limits updated to reflect current batches on market.

Bacterial endotoxins: test removed according to Ph. Eur. policy.

Impurities: impurities G and H added.

Benzympenicillin sodium (0114)

Definition: means of production amended and lower content limit adjusted based on revised limits for total impurities.

Characters: appearance and solubility updated.

Identification: TLC test updated in line with current Style guide.

Appearance of solution: test introduced as substance can be for parenteral use.

Specific optical rotation, Absorbance: tests removed as deemed no longer required based on improved LC for related substances.

Related substances: improved LC introduced allowing for identification of 2 additional impurities; impurity limits updated to reflect current batches on market.

Bacterial endotoxins: test removed, according to Ph. Eur. policy.

Impurities: impurities G and H added.

Cellulose acetate (0887)

Identification (IR): solvent modified to ensure adequate solubility.

Cholesterol for parenteral use (2397)

Benzoyl ureas: 'rotary evaporator' replaced by 'evaporate by suitable means'.

Colistimethate sodium (0319)

Chemical formula: parent structure introduced to show disubstitution at N⁴ in 2 to 5 of the DAB residues.

Definition: updated to reflect the current understanding of the substance's molecular structure.

Production: section introduced to control the composition and purity of colistin starting material.

Identification: former tests A, B and C replaced by test for composition.

Specific optical rotation: test removed as the substance is adequately controlled by the tests for composition and related substances.

Composition, Related substances: LC method introduced which is capable of separating and quantifying the polymyxin components and impurities; limits for the components CMS E1ASM8, CMS E1ASM6, CMS E1ASM4, CMS E2ASM8, CMS E2ASM6, CMS E2ASM4 and also limits for any other impurity and sum of impurities introduced based on available batch data.

Total sulfite: test removed.

Ethylcellulose (0822)

Definition: possibility of adding antioxidants is now stated.

Identification A: sample preparation added.

Assay: chromatographic conditions modified to involve the use of a wide-bore capillary GC column instead of a packed column.

Functionality-related characteristics (FRCs): section added for ethylcellulose used as binder and film former.

Glycerol monostearate 40-55 (0495)

Functionality-related characteristics: this section has been added. Glycerol monostearate 40-55 is used as matrix former in prolonged-release oral solid dosage forms and as consistency agent in dosage forms for cutaneous application. For use as matrix former, the tests for composition of fatty acids, powder flow and particle-size distribution are cross-referenced. For use as consistency agent, the test for composition of fatty acids is cross-

referenced. Due to potential transformations of the crystalline state, the functionality may be altered depending on the manufacturing process conditions; consequently for both uses general chapter 2.2.34. *Thermal analysis* is cross-referenced.

Human plasma (pooled and treated for virus inactivation) (1646)

Plasma pool tests: 2 new BRPs for NAT testing of Hepatitis A virus RNA and Hepatitis E virus RNA have been added to the monograph.

Imatinib mesilate (2736)

Characters: description of appearance updated to cover the amorphous form.

Water: limit increased to 3.0 per cent to also cover the amorphous form.

Manganese sulfate monohydrate (1543)

Identification B: ammonium sulfide solution R replaced by sodium sulfide solution R.

Minocycline hydrochloride dihydrate (1030)

CAS number: updated.

Content: limits revised in line with new LC method used in assay.

Identification: 2 identification series introduced, one using infrared absorption spectrophotometry; previous identification test B no longer necessary, since both identification series are sufficiently specific.

Related substances, Assay: improved LC method introduced; limits for impurities set for newly specified impurities and for any other impurities; limit for total impurities revised.

Water: sample size reduced.

Impurities: new impurities added.

Netilmicin sulfate (1351)

Content: limits proposed with reference to LC for assay.

Specific optical rotation: test removed as purity is controlled by the updated LC for related substances.

Related substances: updated LC method using pulsed electrochemical detection introduced for improved separation of netilmicin and related substances; limits updated based on current market quality.

Bacterial endotoxins: removed as limits to be based on the daily dose of the finished product.

Assay: microbiological assay (2.7.2) replaced by LC method using UV detection.

Impurities: additional impurities specified.

Omega-3-acid ethyl esters 90 (1250)

Definition: content of EPA and DHA ethyl esters revised.

Production: limits for polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDF), dioxin-like polychlorinated biphenyls (DLPCBs), non-dioxin-like PCBs (NDLPCBs; 7PCB), and polybrominated diphenyl ethers (PBDEs) have been added.

Peroxide value: method A replaced by method B to avoid the use of chloroform.

Unidentified fatty acid ethyl esters: limits for 'largest single unidentified peak' and 'total unidentified fatty acid ethyl esters' included.

Cholesterol: test introduced.

EPA and DHA ethyl esters: chromatogram updated to include identification of additional peaks.

Povidone (0685)

Local requirements added in context of harmonisation of pharmacopoeias (chemical formula and chemical structure).

Pregabalin (2777)

Characters: solubility in acetonitrile deleted.

Related substances: preparation of reference solution (b) amended in the test for non-polar impurities.

Proguanil hydrochloride (2002)

Identification: reference spectrum replaced by a reference substance; test B in 1st identification deleted.

Chloroaniline: test deleted as the substance is now controlled by the new method for related substances.

Related substances: new LC method introduced to allow control of chloroaniline and additional impurities; peak-to-valley ratio included as system suitability criterion; limits updated in view of recent batch data.

Impurities: transparency list updated.

Propylene glycol dilaurate (2087)

Assay: calculation formulas modified to take account of the water content for the calculation of the content of monoesters and diesters; free fatty acids are co-eluted with monoesters and this is also reflected in the modified calculation formulas.

Ranitidine hydrochloride (0946)

Related substances: text published in Supplement 8.7 revised to now list impurities B, C, D, E, F, G, H and I as unspecified, based on current batch data; quantitative expression of acceptance criteria introduced; reference solution (d) deleted as impurities D and H are no longer specified.

Sildenafil citrate (2270)

Related substances: new LC introduced to control additional impurities.

Sulfated ash: mass of the substance to be examined modified in accordance with general chapter 2.4.14.

Sucralose (2368)

Related substances: TLC updated.

Xanthan gum (1277)

Content: nomenclature corrected.

pH: carbon dioxide-free water R used as solvent.

2-Propanol: stationary phase corrected.

Other polysaccharides: test deleted.

Microbial contamination: deleted as covered by chapter 5.1.4.

Viscosity: spindle dimensions and distance corrected; sample amount takes loss on drying into account.