Comments concerning revised texts published in the 8th Edition (8.0)

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the March 2013 session and published in the 8th Edition (8.0).

When a text has been technically revised, this is indicated by horizontal or vertical lines in the margin of the supplement and the details given below completes this information. The information below is, however, not necessarily exhaustive.

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

GENERAL CHAPTERS

2.2.40. Near-infrared spectroscopy

General revision to introduce process analytical technology (PAT) concepts such as in- and on-line measurements. Furthermore, duplication with EMA text “Guideline on the use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations” (under revision) has been avoided.

2.2.66. Detection and measurement of radioactivity

The general chapter deals with the theoretical and practical aspects of detection and measurement of radioactivity in the context of Ph. Eur. monographs on radiopharmaceutical preparations.

The general monograph Radiopharmaceutical preparations (0125) contained a section dealing with the measurement of radioactivity, which was more focused on the theoretical aspects and left room for interpretation. In order to give clearer instructions to users, a separate general chapter has been created, describing for example how to choose appropriate instrumentation and instrumental settings, and how to perform calibrations. As a consequence of the introduction of this general chapter, the section on measurement of radioactivity in the general monograph Radiopharmaceutical preparations (0125) has been replaced by a cross-reference to this general chapter.

2.4.25. Ethylene oxide and dioxan

**Methods A and B - reference solutions**: amount of analyte used to spike sample is equal to amount present in a sample at upper test limit (10 ppm).

**Precision (dioxan)**: limit widened to 15 per cent, like ethylene oxide.

**Reagents**: commercially available solutions of ethylene oxide in methylene chloride or in methanol are described.
2.6.31. Microbiological examination of herbal medicinal products for oral use and extracts used in their preparation

General chapter revised to introduce sections dealing with growth-promoting and inhibitory properties of media, test suitability and negative controls.

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

Identification A: requirement for elasticity deleted since test cannot be performed on all types of rubber closures; identifications B and C renamed A and B respectively.

Identification B: possibility of recording FTIR-ATR spectra directly on surface of sample introduced.

Identification C: limit adapted and now depends on total ash content of type sample.

Solution S: water for injections R replaced with water R; use of another container for preparation of solution S added.

Volatile sulfides: description of preparation of standard solution revised.

5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use

Table 5.1.4.-1: as a consequence of the revision of the monograph Premixes for medicated feeding stuffs for veterinary use (1037), also published in the 8th Edition (8.0), specific criteria have been introduced for these premixes. Some of these premixes use excipients of pharmacopoeial quality such as lactose; in this case microbiological quality is controlled according to the acceptance criteria recommended for preparations for oral use; other premixes use excipients of natural origin (e.g. soya bean husks, maize meal, etc.) for which antimicrobial treatment is not feasible; in this case, a higher bioburden is tolerated and specific acceptance criteria are given for TAMC, TYMC and specified micro-organisms in Table 5.1.4.-1; these criteria are based on the microbiological quality of premixes currently approved in Europe.

5.1.8. Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation

This general chapter has been revised to include acceptance criteria for the microbiological quality of extracts intended to be incorporated into herbal medicinal products for oral use. This is because the general monograph Extracts (0765), which is currently undergoing revision, will contain a cross-reference to chapter 5.1.8. The revised chapter clarifies the primary acceptance criteria applicable for such extracts, and it is only where it can be clearly demonstrated that it is not feasible to meet these criteria that an alternative set of criteria may be applied.

5.8. Pharmacopoeial Harmonisation

Additional information is presented as well as sub-sections regarding 7 monographs on excipients.
GENERAL MONOGRAPHS

Radiopharmaceutical preparations (0125)

*Measurement of radioactivity*: as a consequence of the creation of general chapter 2.2.66. *Detection and measurement of radioactivity*, section replaced by cross-reference to general chapter 2.2.66.

DOSAGE FORMS

Parenteral preparations (0520)

*Implants*: it is considered that the release of the active substances from the implant is a critical quality parameter that should be assessed; a Tests section has therefore been added.

Premixes for medicated feeding stuffs for veterinary use (1037)

*Microbial contamination*: the previous version of the monograph did not refer to specific requirements for the evaluation of the microbiological quality of medicated premixes, which led to various interpretations among users of the Ph. Eur.; it is considered that, although medicated premixes are used in an agricultural environment, which has an inherently high bioburden, the microbiological quality of the premix for the duration of its shelf-life must be addressed; reference to general chapter 5.1.4. *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use* has therefore been introduced in the Production section; specific criteria have been introduced in general chapter 5.1.4, also revised for the 8th Edition (8.0).

*Labelling*: additional labelling statements referring to granulation and application of temperature have been introduced.

Tablets (0478)

*Chewable tablets*: further to incidents of chewable tablets being too hard to be easily crushed, section introduced containing definition and production paragraphs.

VACCINES FOR VETERINARY USE

Aujeszky’s disease vaccine (live) for pigs for parenteral administration (0745)

*Embryonated hens’ eggs* (formerly section 2-2-1): method of production deleted.

*Safety test in piglets* (section 2-3-1): this was not the general safety test but a test to characterise the strain (carried out using the vaccine virus at the least attenuated passage level that will be present between the master seed lot and a batch of the vaccine). This justified retaining a higher number of animals, overdose in pregnant animals, etc. VICH requirements did not apply in this case. The test was not modified and the title was changed to clarify this.
Increase in virulence (section 2-3-4): general requirements for performance of test described in general chapter 5.2.6. Evaluation of safety of veterinary vaccines and immunosera; test amended to harmonise with VICH Guideline 41: 4 passages required instead of 5; when the organism is not recovered from any intermediate in vivo passage, the passage is repeated, but in 10 animals; 2 animals for each of 5 passages replaced by a minimum of 2 animals used for the first 4 groups, and a minimum of 8 animals used for the last group; the comparison is no longer made with a control group included in the trials.

Identification (section 3-1): the serological method is given as an example of a suitable method.

Target-animal batch safety test (formerly section 3-5): test deleted.

Rabies vaccine (live, oral) for foxes and raccoon dogs (0746)

Safety, Immunogenicity: since the 1st publication of the monograph in the 1980’s, wildlife rabies epidemiology in Europe has changed. At that time mainly foxes were responsible for transmission of rabies. In the last years, in particular in Eastern Europe, rabid raccoon dogs have been frequently diagnosed. Raccoon dogs may sustain a cycle of wildlife rabies in the same way as is known for foxes. Therefore vaccination of raccoon dogs is used as a tool for eradication of rabies. The scope of the monograph Rabies vaccine (live, oral) for foxes (Vulpes vulpes) has therefore been extended to raccoon dogs (Nyctereutes procyonoides) and tests for safety and immunogenicity for raccoon dogs have been added when raccoon dogs are a target species.

Choice of vaccine virus: molecular biology techniques, in particular gene sequencing, have evolved since the 1st publication of the monograph. Gene sequencing is an essential tool for characterising virus strains and it is of great utility in differentiating between adapted and pathogenic rabies virus strains. Characterisation of the virus strain by gene sequencing has been added to the section Choice of vaccine virus.

Bait stability: added in order to increase awareness among users of the monograph regarding this unique aspect of this vaccine (vaccine incorporated in bait to attract the target species) and its unique method of administration (vaccine released in the fox and/or raccoon dog habitat and taken up actively by the target animals); the section describes tests for the physical stability of the bait casing and thermal stability of the vaccine virus.

Genetic marker and biomarker: added to the definition and relevant tests have also been added (see sections 2-3-2 and 3-7).

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Alovudine (18F) injection (2460)

[18F]Alovudine, also known as [18F]fluorodeoxythymidine or [18F]FLT, is used in positron emission tomography studies since it mirrors cellular proliferation, which is an important parameter in the assessment of response to cancer treatment. The frequency of application is very low, ranging from once to a few times per lifetime.
The radionuclide fluorine-18 is most commonly produced by proton irradiation of water enriched in oxygen-18.

\[^{18}\text{F}\]\text{Allovudine} is mostly prepared by phase-transfer-catalysed nucleophilic substitution of a suitable precursor such as 3-N-Boc-1-[5-O-(4,4′-dimethoxytrityl)-3-O-nitrophenylsulfonyl-2-deoxy-β-D-lyxofuranosyl]thymidine with \[^{18}\text{F}\]\text{fluoride}. Generally, \[^{18}\text{F}\]\text{fluoride} is adsorbed on an anion-exchange resin and eluted with a solution of potassium carbonate, which is then evaporated to dryness. Addition of a phase-transfer catalyst, such as aminopolyether or tetrabutylammonium hydroxide, is used to enhance the nucleophilicity of \[^{18}\text{F}\]\text{fluoride} so that it reacts easily with the precursor at elevated temperature. Hydrolysis of the protective groups using for example trifluoroacetic acid yields \[^{18}\text{F}\]\text{alovudine}. The preparation can be purified by LC, for instance on octadecyl end-capped silica gel.

**Fludeoxyglucose (\(^{18}\text{F}\)) injection (1325)**

*Impurity B*: reference solution (b) and test solution diluted by a factor of 5 to ensure that the limit falls within the linear range.

*Impurity C*: description of preparation of reference solutions modified to take into account that the reagent tetrabutylammonium hydroxide contains 30 molecules of water per molecule of tetrabutylammonium hydroxide.

**Fluoromisonidazole (\(^{18}\text{F}\)) injection (2459)**

\[^{18}\text{F}\]\text{Fluoromisonidazole}, also known as \[^{18}\text{F}\]\text{FMISO}, is used as an imaging agent to assess tumour hypoxia and myocardial ischaemia. The frequency of application is very low, ranging from once to a few times per lifetime.

The radionuclide fluorine-18 is most commonly produced by proton irradiation of water enriched in oxygen-18.

\[^{18}\text{F}\]\text{Fluoromisonidazole} is mostly prepared by phase-transfer-catalysed nucleophilic substitution of a suitable precursor such as 1-(2′-nitro-1′-imidazolyl)-2-O-tetrahydropyranyl-3-O-toluenesulfonyl-propanediol with \[^{18}\text{F}\]\text{fluoride}. Generally, \[^{18}\text{F}\]\text{fluoride} is adsorbed on an anion-exchange resin and eluted with a solution of potassium carbonate, which is then evaporated to dryness. Addition of a phase-transfer catalyst, such as aminopolyether or tetrabutylammonium hydroxide, is used to enhance the nucleophilicity of \[^{18}\text{F}\]\text{fluoride} so that it reacts easily with the precursor at elevated temperature. Hydrolysis under acidic conditions using for example diluted hydrochloric acid yields \[^{18}\text{F}\]\text{fluoromisonidazole}. The preparation can be purified by LC, for instance on octadecyl end-capped silica gel.

**HERBAL DRUGS AND HERBAL DRUG PREPARATIONS**

**Bistort rhizome (2384)**

*Identification B*: illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.
Capsicum (1859)

**Nonivamide, Assay.** Due to the fact that the capsaicin CRS contains small amounts of nonivamide, which would result in an underestimation of the nonivamide content, a separate reference solution (b) has been introduced; the nonivamide and assay calculation formulas have been adapted accordingly. The column description has also been updated.

Capsicum oleoresin, refined and standardised (2336)

**Nonivamide, Assay.** Due to the fact that the capsaicin CRS contains small amounts of nonivamide, which would result in an underestimation of the nonivamide content, a separate reference solution (b) has been introduced; the assay calculation formula has been adapted accordingly. The column description has also been updated.

Capsicum soft extract, standardised (2529)

**Nonivamide, Assay.** Due to the fact that the capsaicin CRS contains small amounts of nonivamide, which would result in an underestimation of the nonivamide content, a separate reference solution (b) has been introduced; the nonivamide calculation formula has been adapted accordingly. The column description has also been updated.

Capsicum tincture, standardised (2337)

**Nonivamide, Assay.** Due to the fact that the capsaicin CRS contains small amounts of nonivamide, which would result in an underestimation of the nonivamide content, a separate reference solution (b) has been introduced; the nonivamide and assay calculation formulas have been adapted accordingly. The column description has also been updated.

Milk thistle dry extract, refined and standardised (2071)

**Assay.** *milk thistle standardised dry extract CRS* renamed *milk thistle dry extract HRS* in accordance with current policy; calculation formula corrected and percentage content of HRS taken into account.

Milk thistle fruit (1860)

**Assay.** *milk thistle standardised dry extract CRS* renamed *milk thistle dry extract HRS* in accordance with current policy and loss on drying no longer explicitly mentioned in calculation formula.

**MONOGRAPH**

Aciclovir (0968)

**Solubility:** solubility in dimethyl sulfoxide deleted and solubility in non-polar solvent (heptane) added.

**Related substances:** specified impurities R and Q (mixture of isomers) added, which co-elute with impurities K and O respectively.

**Bacterial endotoxins:** test added.
Alfacalcidol (1286)

**Related substances**: stationary phase and flow rate modified to improve separation of impurity A; limits updated based on current batch data; general acceptance criterion for unspecified impurities introduced; disregard limit decreased to 0.05 per cent in line with general monograph *Substances for pharmaceutical use* (2034).

**Assay**: now explicitly stated that pre-alfacalcidol resulting from reversible isomerisation in solution contributes to activity, so corresponding peak may be considered, if necessary, in calculation of content.

Brompheniramine maleate (0977)

**Identification**: 1st identification limited to tests C and F as these are considered sufficient.

**Related substances**: CRS for identification of impurity C introduced; packed column replaced by capillary column; disregard limit tightened in line with general monograph *Substances for pharmaceutical use* (2034); impurity B ((S)-enantiomer) removed as it is covered by impurity A (racemate).

Cefradine (0814)

**Related substances**: content of cyclohexa-1,4-dienylglycine (impurity B) in cefradine is now determined against a 1 per cent dilution of the test solution of cefradine using reference solution (c) and a correction factor of 3.4.

Cysteine hydrochloride monohydrate (0895)

**Definition**: scope of monograph added.

**Identification E**: replaced by more-specific test.

**Ninhydrin-positive substances**: TLC replaced by chromatography using amino acid analyser that also allows quantification of ammonium.

**Heavy metals**: method A replaced by method G.

Dexamethasone (0388)

**Related substances**: based on recent batch data, 2 additional specified impurities introduced; stationary phase description modified for consistency reasons.

**Impurities**: transparency list updated.

Dextranomer (2238)

**Loss on drying**: usual direct drying procedure now applied.

Dipyridamole (1199)

**Related substances**: peak-to-valley ratio description updated (calculation based on minor peak).

Doxapram hydrochloride (1201)

**Characters**: solubility information updated.

**Identification**: sample preparation for IR deleted, in line with current policy.
**Solution S**: solution diluted to ensure complete dissolution.

**Ethylcellulose (0822)**

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

**Fenbendazole for veterinary use (1208)**

*Identification*: method of sample preparation no longer specified.

*Related substances*: statement added on conditions for preparation of solutions; relative retentions and identification of specified impurities introduced; total impurities now only expressed as a percentage; disregard limit raised.

**Finasteride (1615)**

*Related substances*: limits revised to reflect quality of substances used in approved medicinal products in Europe; new expression of acceptance criteria now applied; stationary phase description modified for consistency reasons.

**Flutamide (1423)**

*Content*: limits updated to reflect change in assay method.

*Solubility*: solubility in non-polar solvent added, in line with Technical guide.

*Related substances*: explicit acceptance criterion for unspecified impurities introduced in line with general monograph *Substances for pharmaceutical use (2034)*; system suitability CRS containing all specified impurities introduced and relative retentions now given; limits updated based on recent batch results; stationary phase description modified for consistency reasons.

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

**Glipizide (0906)**

*Related substances*: gradient modified to elute all specified impurities; total impurities now only expressed as a percentage.

**Heparins, low-molecular-mass (0828)**

Monograph aligned with recently revised monographs *Heparin sodium (0333)* and *Heparin calcium (0332)*.

*Production*: statement about parenteral administration deleted as unfractionated heparin monographs now only cover a single quality suitable for parenteral administration; tests for nucleotide and protein impurities of source material deleted since they are redundant with respect to unfractionated heparin monographs.

*Sodium*: range modified further to comments received during public enquiry on monograph *Heparin sodium (0333)*, to reflect current batch data.

*Heavy metals*: method C replaced by method F as in unfractionated heparin monographs, in line with current policy.
Human plasma for fractionation (0853)

*Individual plasma units*: questions have arisen amongst some users of the monograph over the reference to freezing plasma intended for the production of non-labile proteins ‘as soon as possible’ after collection. This is because time limits of 24 h (plasma obtained from plasmapheresis) and 72 h (plasma obtained from whole blood) are also given for freezing. For clarification, the reference to ‘as soon as possible’ has been deleted and the monograph now states the maximum acceptable time limits for freezing of plasma following collection. Additionally, in the context of using suitable methods to conserve labile proteins as much as possible, the reference to good manufacturing practice (GMP) has been deleted because there are steps taken that do not necessarily fall under the scope of GMP which contribute to the quality of plasma and the conservation of labile proteins.

Human α-1-proteinase inhibitor (2387)

*Bacterial endotoxins*: test introduced in monograph as an alternative to rabbit pyrogens test in line with effort to implement 3Rs policy. According to general chapter 5.1.10. *Guidelines for using the test for bacterial endotoxins*, the endotoxin limit is defined on the basis of dose by K/M, where K is the threshold pyrogenic dose endotoxin per kilogram of body mass and M is the maximum recommended bolus dose of product per kilogram of body mass. In this case, K is given with 5 IU/kg of body mass in Table 5.1.10.-1 and M is 60 mg/kg according to the Summary of product characteristics. This results in 0.08 IU/mg for the maximum allowed bacterial endotoxins content.

Hydrocortisone acetate (0334)

*Related substances*: acidic solvent mixture introduced for stability reasons; description of test and reference solutions modified accordingly; concentration of test solution (a) decreased to avoid peak saturation.

Hypromellose (0348)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

*Functionality-related characteristics (FRCs)*: tests for viscosity and degree of substitution moved back to the mandatory part of the monograph with a cross-reference in the FRC section.

Levonorgestrel (0926)

*Related substances*: 2nd LC method introduced to allow control of additional impurities.

*Impurities*: impurities V and W added.

Lomustine (0928)

*Content*: limits revised.

*Identification*: 2nd identification series deleted due to high toxicity of compound in order to limit unnecessary handling.

*Related substances*: TLC and LC replaced by single LC; impurities A, B and C now listed as other detectable impurities.
Maize starch (0344)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. Pharmacopoeial harmonisation.

Identification A: illustration of maize starch added.

Mannitol (0559)

This revised monograph is the result of the International Harmonisation process.

Definition: new limits included based on batch data and taking into account the total amount of impurities.

Characters: description corrected.

Identification C: procedure improved to allow use of common microwave ovens.

Identification D: silica gel containing inorganic binder replaced by silica gel containing organic binder.

Melting point: test included and cross-reference added under Identification.

Reducing sugars: Japanese Pharmacopoeia method for total sugars adapted to cover only reducing sugars; limit halved.

Lead/heavy metals: test for lead replaced by test for heavy metals.

Nickel: method improved.

Megestrol acetate (1593)

Related substances: based on recent batch data, limit for impurity K increased; in addition, correction factor introduced for same impurity; stationary phase description modified for consistency reasons.

Metformin hydrochloride (0931)

Identification B: description of sample preparation deleted.

Appearance of solution: preparation of solution modified.

Impurity F: additional test introduced because impurity (N-methylmethanamine) not controlled by test for related substances.

Related substances: since maximum daily dose is > 2 g/day, limit for unspecified impurities adapted to requirements of general monograph Substances for pharmaceutical use (2034); limit for total and disregard limit added.

Methylcellulose (0345)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. Pharmacopoeial harmonisation.
**Functionality-related characteristics (FRCs):** tests for viscosity and degree of substitution moved back to the mandatory part of the monograph with a cross-reference in the FRC section.

**Methylprednisolone (0561)**

**Content:** upper limit updated to reflect change in assay method.

**Identification:** TLC in 1st identification series (identification test B) replaced by cross-reference to LC for assay.

**Specific optical rotation:** dioxan replaced by less-toxic solvent ethanol (96 per cent).

**Related substances:** LC revised to allow separation of additional impurities; in line with general monograph *Substances for pharmaceutical use* (2034), explicit criterion for unspecified impurities introduced; in addition, limits updated to reflect quality of substances used in medicinal products on European market.

**Assay:** UV absorbance replaced by LC.

**Impurities:** new transparency list introduced, dividing impurities into specified and other detectable.

**Metoprolol succinate (1448)**

**Related substances:** amount of *metopropol impurity A CRS* used in reference solution (a) decreased; stationary phase description modified for consistency reasons.

**Metoprolol tartrate (1028)**

**Related substances:** amount of *metoprolol impurity A CRS* used in reference solution (a) decreased; stationary phase description modified for consistency reasons.

**Minoxidil (0937)**

**Content:** lower limit tightened.

**Identification:** identification A deleted from 1st identification as IR alone is sufficient.

**Appearance of solution:** test deleted in line with current policy.

**Related substances:** new LC procedure introduced; limits revised in view of quality of current products.

**Impurities:** impurities C and D removed from transparency list as they have not been reported in batches examined.

**Nicotine ditartrate dihydrate (2599)**

**Water:** lower limit revised; sample weight reduced.

**Oxfendazole for veterinary use (1458)**

**Related substances:** total impurities now only expressed as a percentage; limit for unspecified impurities and disregard limit adapted to requirements of general monograph *Substances for pharmaceutical use* (2034).
Peritoneal dialysis, solutions for (0862)

**Aluminium.** In the monograph *Solutions for haemofiltration and haemodiafiltration* (0861) (HFS), the limit for aluminium is 10 µg/L, whereas in *Solutions for peritoneal dialysis* (0862) (PDS) it is 15 µg/L; considering the volumes administered to patients, such a difference between the monographs does not appear to be justified. Moreover, with the development of continuous ambulatory peritoneal dialysis, patients might receive larger volumes of fluid than in standard peritoneal dialysis. Therefore the limit for aluminium in the PDS monograph was harmonised with that in the HFS monograph, i.e. 10 µg/L. As a consequence, the volume of the solution to be examined has been increased from 400 to 600 mL.

**Bacterial endotoxins:** the limit has been lowered from 0.25 IU/mL to 0.05 IU/mL.

- *peritoneal dialysis (PD)* is a continuous treatment whereby most patients receive 2 L, 4 times daily (8 L per day); some patients receive 10 L per day (automated PD);
- *during hemodialysis,* patients receive large volumes of fluid, but the hemodialysis fluid is separated from the body by an artificial membrane;
- *in PD,* the fluid administered is separated from the bloodstream by a biological membrane (the peritoneum), which in case of inflammation is more permeable for foreign substances;
- *PD fluids are continuously infused to patients* (24 hours a day), whereas haemodialysis patients are treated 3 times per week for a limited number of hours; PD fluids are therefore infused in larger volumes and the endotoxins level has to remain as low as possible to ensure patient safety.

Supposing 100 per cent bioavailability of endotoxins: maximum acceptable dose of endotoxin for a 70 kg patient is 350 IU/h. For a PD fluid load of 8 L per day, this means 333 mL/h. The maximum theoretical acceptable endotoxin concentration would be 350 IU/333 mL = 1.05 IU/mL, considering the guidance for calculation of acceptable bacterial endotoxins dose given in general chapter 5.1.10. *Guidelines for using the test for bacterial endotoxins.* For a 50 kg patient receiving 10 L via automated PD, this value would be reduced to 0.75 IU/mL. However, general chapter 5.1.10 is based on incidental admissions of a relatively short duration (a few days to a few weeks) to a hospital where products are administered intravenously. PD treatment is a continuous treatment whereby patients receive daily PD fluids in large volumes for years and the approach developed in general chapter 5.1.10 would not be applicable to this particular case. In addition, cases of aseptic peritonitis have been reported with endotoxin levels lower than that currently accepted, i.e. 0.25 IU/mL. Therefore, it seems reasonable to lower the limit, the objective being to reduce the patient’s cumulated exposure to endotoxins as much as technically possible. Moreover, endotoxins are remains of bacteria present in the production system. Therefore, by setting a low limit for endotoxins, a stricter control over the production process would be applied, which would act as an indicator of low levels of contamination. The limit of 0.05 IU/mL was chosen because this is technically achievable with the current production systems.

Comments received during the public enquiry proposed to take into account solutions that cannot fulfill the bacterial endotoxin limit of 0.05 IU/mL, not because they are contaminated with bacterial endotoxins, but because they contain maltodextrin inducing a matrix effect that interferes with the validation of the LAL method. As a consequence, the validation of the LAL method cannot be done for a bacterial endotoxin limit lower than 0.14 IU/mL. To take this into account, ‘unless otherwise justified and authorised’ has been added to the requirement.

**Lactate and hydrogen carbonate:** helium R replaced by helium for chromatography R.
Phytomenadione (1036)

Identification: test B now refers to LC used for related substances test and assay since TLC now only used for impurity A.

Related substances: TLC replaced by LC in line with current policy, except for impurity A (menadione).

Assay: method replaced by LC used for related substances test.

Potato starch (0355)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. Pharmacopoeial harmonisation.

Identification A: illustration of potato starch added.

Proline (0785)

Definition: scope of monograph added.

Ninhydrin-positive substances: TLC replaced by chromatography using amino acid analyser that also allows quantification of ammonium.

Assay: end-point determination by colour indicator replaced by potentiometric determination.

Serine (0788)

Definition: scope of monograph added.

Ninhydrin-positive substances: TLC replaced by chromatography using amino acid analyser that also allows quantification of ammonium.

Assay: end-point determination by colour indicator replaced by potentiometric determination.

Sulfadiazine (0294)

Heavy metals: test H found suitable.

Threonine (1049)

Definition: scope of monograph added.

Ninhydrin-positive substances: TLC replaced by chromatography using amino acid analyser that also allows quantification of ammonium.

Heavy metals: method C replaced by method G.

Timolol maleate (0572)

Enantiomeric purity: quantity of CRS reduced; stationary phase description modified.

Related substances: LC column replaced by more efficient one.
Valine (0796)

Definition: scope of monograph added.

Ninhydrin-positive substances: TLC replaced by chromatography using amino acid analyser that also allows quantification of ammonium.

Assay: end-point determination by colour indicator replaced by potentiometric determination.

Heavy metals: method D replaced by method H.

Wheat starch (0359)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. Pharmacopoeial harmonisation.

Identification A: illustration of wheat starch added.