Comments concerning revised texts published in Supplement 8.4

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the March 2014 session and published in Supplement 8.4. 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

2.4.25. Ethylene oxide and dioxan

**Method A:** volume of dioxan solution used to prepare reference solution (a) increased from 0.1 mL to 0.5 mL in order to introduce identical volumes of the test solution and reference solution (a) in the head-space vial. A new reagent ‘dioxan solution R2’ (0.02 mg/mL) has, in parallel, been created so that the absolute quantity of dioxan added to reference solution (a) remains unchanged.

2.6.25. Avian live virus vaccines: tests for extraneous agents in batches of finished product

**Routine tests:** the following procedures may be performed when the vaccine virus cannot be neutralised in the yolk sac inoculation test:

- for enveloped viruses such as avian infectious bronchitis virus (AIBV) and Newcastle disease virus (NDV) a detergent/lipid solvent (such as chloroform) may be used to neutralise the virus before inoculating it into the yolk sac,
- use appropriate tests to detect avian encephalomyelitis virus and avian nephritis virus. In the case of avian nephritis virus, the test in chicken kidney cells described in section 2 of general chapter 2.6.24. *Avian viral vaccines: tests for extraneous agents in seed lots* is suitable.

If the vaccine virus cannot be completely neutralised - using monospecific antiserum - for the yolk sac inoculation test, the test in chicks is not appropriate.

Furthermore, manufacturers must justify the use of alternative solutions when complete neutralisation is not possible.

**Tests done once in the lifetime of a vaccine:** the vaccine must be inoculated by the yolk sac route in all cases since this is an important means of detecting unknown viruses. In the
event of difficulties, manufacturers must find alternative solutions to be able to apply this test, for example by producing in-house the appropriate sera for neutralisation.

3.1.1.1. Materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components

Production: information on additives updated; reference to colourant ultramarine blue deleted.

Tests: water for injections R replaced by water R.

Plastic additives 01, 04 and 05: concentration of reference solutions increased for better visibility of spots; TLC plate replaced.

Plastic additive 03: option to record IR spectrum of residue between 2 plates transparent to IR radiation or by ATR added in case amount of residue is insufficient to prepare disc.

Assay: method revised to avoid use of dibutyl phthalate R.

3.1.1.2. Materials based on plasticised poly(vinyl chloride) for tubing used in sets for the transfusion of blood and blood components

Plastic additive 01: TLC plate replaced.

3.1.10. Materials based on non-plasticised poly(vinyl chloride) for containers for non-injectable, aqueous solutions

Production: information on colourants updated.

Identification: absorption maxima revised and tolerance added.

Assay: method revised to avoid use of dibutyl phthalate R.

3.1.11. Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration

Production: component II of plastic additive 23 added as separate additive (tin-stabiliser); information on colourants updated.

Identification: absorption maxima revised and tolerance added.

Assay: method revised to avoid use of dibutyl phthalate R.

3.1.14. Materials based on plasticised poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion

Production: information on additives updated.

Tests: water for injections R replaced by water R.

Plastic additives 01, 04 and 05: concentration of reference solutions increased for better visibility of spots; TLC plate replaced.

Plastic additive 03: option to record IR spectrum of residue between 2 plates transparent to IR radiation or by ATR added in case amount of residue is insufficient to prepare disc.

Assay: method revised to avoid use of dibutyl phthalate R.
3.2.1. Glass containers for pharmaceutical use
It has been decided to further emphasise the need for control of specific components that may be toxic for chronic use and for vulnerable patient groups. The statements in the definition section of Parenteral preparations (0520), in chapter 3.2.1. Glass containers for pharmaceutical use and in chapter 3.2.2. Plastic containers and closures for pharmaceutical use have therefore been supplemented.

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5.8. Pharmacopoeial harmonisation
Additional information is presented for 3 monographs on excipients.

5.12. Reference standards
General revision to update chapter to reflect recent advances in pharmaceutical reference standards, including harmonisation with the specifications and definitions of the corresponding ISO Guides (i.e. ISO Guides 30 and 34) and introduction of:
- the definition of international standards based on WHO Technical Report Series 932,
- herbal reference standards (HRS),
- biological reference preparations (BRP) and chemical reference substances for biologicals.

Minor editorial changes have also been made throughout the text.

DOSAGE FORMS

Parenteral preparations (0520)
It has been decided to further emphasise the need for control of specific components that may be toxic for chronic use and for vulnerable patient groups. The statements in the definition section of Parenteral preparations (0520), in chapter 3.2.1. Glass containers for pharmaceutical use and in chapter 3.2.2. Plastic containers and closures for pharmaceutical use have therefore been supplemented.
VACCINES FOR VETERINARY USE

Brucellosis vaccine (live) (Brucella melitensis Rev. 1 strain) for veterinary use (0793)

*Choice of vaccine strain:* deletion of the reference to an immunogenicity test performed in the target species.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Technetium ($^{99m}$Tc) etifenin injection (0585)

*Definition:* information on the mode of preparation deleted and added to the knowledge database.

*Identification B:* test revised in order to identify the complex of technetium-99m with etifenin instead of the ligand etifenin.

*Physiological distribution:* test deleted as all remaining tests considered sufficient to confirm identity and quality of the preparation.

*Bacterial endotoxins:* test with specified limit introduced.

*Radiochemical purity:* test revised as previous TLC stationary phase no longer commercially available.

MONOGRAPHS

Alprostadil (1488)

*Identification B:* sample preparation deleted.

*Related substances, Assay:* quantity of alprostadil CRS reduced.

Ammonium bromide (1389)

*Chlorides and sulfates:* quantitative expression of acceptance criteria, since content used in assay calculation.
Arachis oil, refined (0263)

*Composition of fatty acids*: a new peanut source has appeared on the market with different fatty acid contents. The limits for oleic acid and linoleic acid have been adjusted so that the arachis oil from this source is covered by the monograph.

Carbidopa (0755)

*Identification C*: sample preparation deleted.

*Related substances*: LC for methyldopa and methylcarbidopa replaced by LC for related substances; limits updated and new specified impurities added.

*Impurities*: section added.

Carisoprodol (1689)

*Related substances*: reference solution (e) modified.

Carrageenan (2138)

*Identification*: identification test A moved to FRC section since labelling of carrageenan type no longer required and identification by metachromasia and by IR considered sufficient; additional information given for identification by IR.

*Heavy metals*: individual limits for arsenic, cadmium, lead and mercury instead of limit for heavy metals (2.4.8).

*Labelling*: section deleted because grades of carrageenans available on market are mixtures of different types of copolymers.

Cetostearyl isononanoate (1085)

*Hydroxyl value*: sample size and volume of acetylating reagent specified.

Chlorhexidine dihydrochloride (0659)

*Characters*: solubility section updated.

*Chloroaniline*: test replaced by absorption spectrophotometry to allow better control of chloroaniline; limit has been tightened.

*Related substances*: new LC method introduced; limits for individual impurities have been added.

Ciprofloxacin (1089)

*Related substances*: quantity of CRS in reference solution (b) decreased.

Ciprofloxacin hydrochloride (0888)

*Related substances*: quantity of CRS in reference solution (b) decreased.

Cocoyl caprylocaprate (1411)

*Hydroxyl value*: sample size and volume of acetylating reagent specified.
Colistin sulfate (0320)

*Composition*: test simplified by using normalisation procedure to calculate content for each of polymyxins E1, E2, E3, E1-I and E1-7MOA and their sum.

Demeclocycline hydrochloride (0176)

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

*Specific optical rotation, Specific absorbance*: tests removed as not required based on improved related substances test.

*Related substances, Assay*: LC method improved to allow for determination of additional impurities.

*Impurities*: section updated.

Detomidine hydrochloride for veterinary use (1414)

*Content*: limits tightened.

*Solubility*: solubility in acetone deleted.

*Identification A*: sample preparation deleted.

*Related substances*: limits revised; reporting threshold increased.

*Water*: test for loss on drying replaced by water and limit increased.

Doxycycline hyclate (0272)

*Specific optical rotation, Specific absorbance*: tests deleted as purity controlled by LC.

*Related substances, Assay*: LC improved; limits for specified impurities adapted and a limit for total impurities introduced.

*Ethanol*: test modified in line with current policy.

Doxycycline monohydrate (0820)

*Identification*: test C replaced by reference to test for water.

*Specific optical rotation, Specific absorbance*: tests deleted as purity controlled by LC.

*Related substances, Assay*: LC improved; limits for specified impurities adapted and a limit for total impurities introduced.

Drospirenone (2404)

*Related substances*: impurity A listed as a specified impurity.

Fluocinolone acetonide (0494)

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

*Related substances*: gradient LC introduced to allow control of additional impurities.

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

*Impurities*: transparency list updated.
Haemodialysis, solutions for (0128)

**Microbial contamination**: a test has been added in case the concentrated haemodialysis solution is not sterile, with the same limit as required for *Water for diluting concentrated haemodialysis solutions* (1167).

**Bacterial endotoxins**: the same limit (less than 0.25 IU/mL) as required for *Water for diluting concentrated haemodialysis solutions* (1167) has been introduced.

Hydralazine hydrochloride (0829)

**Assay**: reference to calomel electrode deleted.

Levamisole for veterinary use (1728)

**Related substances**: the amount of CRS needed to prepare reference solution (a) has been decreased.

Levamisole hydrochloride (0726)

**Related substances**: the amount of CRS needed to prepare reference solution (a) has been decreased.

Lisinopril dihydrate (1120)

**Solubility**: section updated.

**Specific optical rotation**: test described under identification section.

**Related substances**: revised LC introduced to control new impurities; limits updated.

**Impurities**: section updated.

Marbofloxacin for veterinary use (2233)

**Absorbance**: borate buffer replaced by ammonium carbonate buffer.

Oxaliplatin (2017)

**Test for impurity D**: *oxaliplatin* CRS replaced by the substance to be examined.

**Assay**: quantity of *oxaliplatin* CRS reduced in reference solution (c).

Potassium bromide (0184)

**Chlorides and sulfates**: quantitative expression of acceptance criteria, since content used in assay calculation.

Rice starch (0349)

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 rice starch added.
Sodium bromide (0190)

*Chlorides and sulfates:* quantitative expression of acceptance criteria, since content used in assay calculation.

Sodium chloride (0193)

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

*Identification A:* only reaction (a) of chlorides used.

Sodium citrate (0412)

*Water:* solvent mixture added.

Sorbitol, liquid (crystallising) (0436)

*Assay:* chromatographic run time modified. Information about the detector temperature added and minimum resolution requirement given with more accuracy.

Sorbitol, liquid (non-crystallising) (0437)

*Assay:* chromatographic run time modified. Information about the detector temperature added and minimum resolution requirement given with more accuracy.

Squalane (1630)

Scope of monograph enlarged to include squalane of synthetic origin; Definition, Identification and Labelling sections amended accordingly.

Stearic acid (1474)

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