

Comments concerning revised texts published in Supplement 10.6

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November session and published in Supplement 10.6.

When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.6. 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

1. General notices

1.4. Monographs, sub-section Tests and assays: new policy for dissolution and disintegration tests included.

2.4.29. Composition of fatty acids in oils rich in omega-3 acids

EPA AND DHA, Step B: the washing of combined extracts with water and drying over anhydrous sodium sulfate is made optional.

2.8.13. Pesticide residues

Qualitative and quantitative analysis of pesticide residues: the natural occurrence of bromide in seaweeds has been added as an example for constituents to be taken into account in the interpretation of results.

2.9.1. Disintegration of tablets and capsules

Test A: Apparatus dimensions given as ranges to reflect the PDG harmonised text.

Test B:

- test procedure harmonised with Test A to allow the operator to proceed in stages;
- tolerances added for the dimensions of the plates of the basket-rack assembly.

The section on Test B has been entirely revised for consistency with Test A.

2.9.27. Uniformity and accuracy of delivered doses from multidose containers

The reference to oral dosage forms has been deleted, but it is not the intention that this general chapter be applied for all dosage forms (e.g. parenteral preparations). As indicated in the General Notices, a general chapter only becomes mandatory when referred to in a monograph.

Accuracy requirement might be given in the monograph referring to this general method.

Possibility to conduct the test based on volume measurements.

2.9.33. Characterisation of crystalline and partially crystalline solids by X-ray powder diffraction (XRPD)

Qualitative phase analysis: the upper angle to record the diffraction pattern has been reduced to at least 30° as there is typically not much information above 30° for organic compounds and to avoid observing double peaks.

Quantitative phase analysis: it has been clarified that in favourable cases amounts of crystalline phases less than 10 per cent may be determined.

3.2.2. Plastic containers and closures for pharmaceutical use

List of commonly used polymers replaced with a cross-reference to Materials used for the manufacture of containers (3.1 and subsections).

Editorial changes have been made throughout the general chapter, including a change in the French title.

5.8. Pharmacopoeial harmonisation

The non-mandatory Functionality-related characteristics section in Ph. Eur. monographs subject to pharmacopoeial harmonisation through the Pharmacopoeial Discussion Group (PDG) is handled as any other local requirement or non-harmonised attribute to avoid confusion of users of the Ph. Eur.

Therefore the general sentence related to the previous situation highlighting that this section is specific to the Ph. Eur. has been deleted.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 2 new monographs published in Supplement 10.6.

GENERAL MONOGRAPHS

Allergen products (1063)

Production.

- In-house reference preparation/Characterisation of the in-house reference preparation. Possibility to use in vitro methods (for the characterisation of the biological potency of 1st in-house reference preparation) in other cases than when not enough patients are available.

Tests

- Protein content. Deletion of the statement on the performance of the test as a batch-to-batch consistency test if the biological potency is determined; as the performance of the test does not depend on the performance of the test for biological potency.

- Aluminium. Clarification of the wording ('unless otherwise justified and authorised' relates to the stated amount, not the maximal dose of 1.25 mg).

Vaccines for veterinary use (0062)

It was clarified in the introductory note that for a product intended for minor use/minor species, the protocols of certain tests may be adapted.

DOSAGE FORMS

Ear preparations (0652)

Definition: addition of clarification that ear preparations are intended for a local effect.

Tests: requirement for the test on uniformity of mass revised.

Ear drops and ear sprays: section separated in two.

Ear sprays: addition of uniformity requirements (uniformity of delivered dose, intra-container testing; uniformity of delivered mass), of number of deliveries per container and of leak rate.

Ear tampons: definition revised.

Eye preparations (1163)

Eye drops and Eye lotions: test for particulate contamination: sub-visible particles (2.9.53) added with corresponding acceptance criteria.

Definition: text states that with the exception of veterinary medicinal products, preparations specifically intended for use in the injured eye are free from preservatives and supplied in single-dose containers.

Ophthalmic inserts: test to demonstrate appropriate dissolution of the active substance(s) moved from the Production section to the Test section.

Foams, medicated (1105)

Editorial changes introduced to align with similar monographs.

Sterility test: test deleted to avoid duplication with the requirement in the respective general dosage form monograph.

Labelling: section deleted to avoid duplication with the requirement in the respective general dosage form monograph.

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Gallium (⁶⁸Ga) edotreotide injection (2482)

Production: nowadays gallium-68 is also produced in cyclotrons. A section has been introduced requiring that gallium (⁶⁸Ga) chloride solution used for the preparation of gallium (⁶⁸Ga) edotreotide injection complies with either the monograph *Gallium (⁶⁸Ga) chloride for radiolabelling (2464)* or the monograph *Gallium (⁶⁸Ga) chloride (accelerator-produced) solution for radiolabelling (3109)*.

Identification: replacement of the test for half-life determination by the test for approximate half-life determination. The limits for the approximate half-life have been set with a tolerance of ± 10 per cent.

pH: limits were widened to take account of the specifications for approved products.

Edotreotide, gallium edotreotide and other related substances: replacement of the gradient LC procedure by an isocratic LC procedure with a system suitability test based on the resolution of gallium edotreotide and edotreotide.

Limit test for HEPES (impurity D): procedure modified and limit widened based upon batch data.

Ethanol: detailed procedure description replaced by cross-reference to general method.

Radionuclidic purity: section refers to the corresponding tests in the monographs of the gallium (⁶⁸Ga) chloride solution for radiolabelling.

Radiochemical purity: replacement of the interconnected tests with an overall limit by 2 separate tests, each having an individual limit.

Impurities: Germanium-68 has been deleted from the list of impurities as it is now controlled via the monograph on *Gallium (⁶⁸Ga) chloride for radiolabelling (2464)*. [⁶⁸Ga]Gallium in colloidal form and the [⁶⁸Ga]gallium (III) ion are indirectly controlled and thus these impurities are no longer mentioned in the transparency list either. HEPES is maintained in the list, as it is the only impurity that is individually quantified by a procedure given in the monograph.

Pentetate sodium calcium hydrate for radiopharmaceutical preparations (2353)

Title: Introduction of “hydrate” in-line with current policy of indicating hydrates in monograph titles.

Identification B: reaction (b) of calcium on the ignited substance does not work as prescribed and has been replaced by reaction (a) on the substance as is.

Impurity A: for the given LC column there is only one kind of specific surface and pore size, so there is no need to give these details.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Atractylodes lancea rhizome (2559)

The synonym 'Atractylodes Japonica Koidz.' has been deleted.

Ganoderma (3001)

Assay: an isocratic step of 5 min has been added at the end of the gradient.

Milk thistle dry extract, refined and standardised (2071)

Assay: peak integration of silibinin B and dihydrosilibinin B clarified.

Milk thistle fruit (1860)

Assay: peak integration of silibinin B and dihydrosilibinin B clarified.

Nettle root (2538)

Foreign matter: specific requirements introduced to take account of harvesting practices and difficulties in differentiating between underground organs and aerial parts.

Olive leaf (1878)

Identification B: legend of illustration of powdered herbal drug introduced into the text of identification B.

Assay: the method is harmonised with the method described in the monograph on *Olive leaf dry extract* (2313).

MONOGRAPHS

Aluminium stearate (1663)

Cadmium, Lead, Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests are deleted.

Definition: the limit for the content of stearic acid in the fatty acid fraction has been decreased to minimum 35.0 per cent based on current batch data.

Aprotinin concentrated solution (0579)

Des-Ala-aprotinin and des-Ala-des-Gly-aprotinin: test was renamed as "Related substances"; capillary zone electrophoresis method was replaced by an HPLC method to control additional impurities; limits for impurities A and B were adjusted accordingly; limits for 6 additional specified impurities, for sum of all impurities eluting after the principal peak and for unspecified impurities were introduced.

Pyroglutamyl-aprotinin and related compounds: additional specified impurity was introduced; reporting threshold and minimum value for symmetry of the main peak were added; *Aprotinin for system suitability CRS* was replaced by *aprotinin solution BRP* as the reference standard in the test method.

Impurities: transparency list was updated.

Benzoyl peroxide, hydrous (0704)

Identification B (IR): minimum transmittance of 40 per cent specified.

Dibenzoyl peroxide: colour indicator replaced by potentiometric end-point determination using a platinum electrode.

Water (2.5.12): test must be performed protected from light.

Bisacodyl (0595)

Identification B by UV spectrophotometry: deleted.

Related substances: impurity D is deleted since it is not present in the production batches.

Bumetanide (1076)

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market.

Butyl parahydroxybenzoate (0881)

This monograph has been revised to indicate its status within the context of International Harmonisation through the Pharmacopoeial Discussion Group (PDG), 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*. Non-harmonised attributes have been placed between black diamonds (◆ ◆), while local requirements only present in the Ph. Eur. text have been placed between white diamonds (◇ ◇).

Calcium carbonate (0014)

Identification B: it is considered sufficient to use only reaction (b).

Calcium gluconate (0172)

Identification B: it is considered sufficient to use only reaction (b).

Calcium gluconate, anhydrous (2364)

Identification B: it is considered sufficient to use only reaction (b).

Calcium hydrogen phosphate (0981)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Calcium hydrogen phosphate dihydrate (0116)

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Calcium hydroxide (1078)

In line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the following impurities will be added: Cadmium (1 ppm) and Lead (1 ppm).

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Calcium phosphate (1052)

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limit. In addition, the following impurity will be added: Lead (1 ppm).

Candesartan cilexetil (2573)

Further to the CHMP* opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 regarding the detection, management and prevention of presence of N-nitrosamines in medicinal products for human use (see assessment report published on 25 June 2020**) and the CHMP* decision to apply these recommendations to “sartans medicinal products” (see news published on 13 November 2020***), a revised version of this monograph is proposed for adoption as a minor revision and publication in Supplement 10.6 to align the Ph. Eur. requirements with the latest regulatory decisions.

Production: section completely reworded; recommendation to perform a risk assessment of the manufacturing process and, if needed, implement a control strategy for the detection and control of N-nitrosamine impurities added.

Tests: Nitrosamines test deleted.

CHMP*: Committee for Human Medicinal Products of the European Medicines Agency

** https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

*** <https://www.ema.europa.eu/en/news/nitrosamines-ema-aligns-recommendations-sartans-those-other-medicines>

Carboplatin (1081)

Related substances: impurity A quantified using the corresponding CRS as external standard.

Cellulose acetate phthalate (0314)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Chenodeoxycholic acid (1189)

Related substances: TLC replaced by 2 different LC methods.

Assay: by potentiometric end-point determination.

Editorial changes made throughout the monograph.

Cholecalciferol concentrate (oily form) (0575)

Identification A: absorption maximum aligned with the one found in the other cholecalciferol concentrate monographs (powder form 574 and water-dispersible form 598).

Assay: hexane class 2 solvent replaced by heptane class 3 solvent.

Cholesterol for parenteral use (2397)

Definition: revised to allow the use of synthetic cholesterol; Test section indicates which tests apply depending on the source of the cholesterol used (derived from wool fat or synthetic).

Identification: section updated.

Related substances: test introduced for synthetic cholesterol.

Bacterial endotoxins: test deleted as covered by the general monograph *Parenteral preparations* (0520).

Copper sulfate pentahydrate (0894)

Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limit. In addition, the following impurities will be added: Cobalt (1 ppm) and Nickel (20 ppm).

Croscarmellose sodium (0985)

Identification: identification by IR added in the context of the revision of the harmonised monograph; identification B deleted; identification of sodium harmonised (preparation of test solution modified compared to previous text).

Settling volume, Degree of substitution: these tests are considered as harmonised within the Pharmacopoeial Harmonisation framework. To have the same legal status in the Ph. Eur., the JP and the USP, they have been moved to the mandatory sections Tests and Assay, respectively, and are referred to under Functionality-related characteristics.

Water-soluble substances: result expressed with reference to the dried substance.

Storage: statement added because substance is hygroscopic.

Crospovidone (0892)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation).

Dapsone (0077)

Related substances: TLC replaced by liquid chromatography. List of impurities added.

Deferiprone tablets (2986)

Dissolution. Test revised to bring it in line with the new policy.

Dimetindene maleate (1417)

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market.

Dipotassium clorazepate monohydrate (0898)

Graphic formula, molecular formula, relative molecular mass and chemical name: corrected in line with the substance being a monohydrate.

Identification: use of CRS added in IR test; second identification testing deleted as the substance is not used in pharmacies.

Related substances: system suitability test optimised; column temperature added.

Dronedarone tablets (3038)

Dissolution. Test revised to bring it in line with the new policy.

Furthermore, additional requirements at levels 2 and 3 included.

Etacrynic acid (0457)

Related substances: in preparation of reference solution (b), volume is expressed using fewer significant figures due to the qualitative use of this solution.

Loss on drying: subsequent to the revision of general method 2.2.32, the reference to diphosphorus pentoxide has been deleted from this test; milder vacuum conditions introduced.

Ethyl parahydroxybenzoate (0900)

This monograph has been revised to indicate its status within the context of International Harmonisation through the Pharmacopoeial Discussion Group (PDG), a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia.

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Ethylcellulose (0822)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Ferrous sulfate, dried (2340)

Chromium, Nickel, Zinc: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the current limit for Chromium and with the updated limits for Nickel and Zinc. In addition, the following impurities will be added: Cobalt (15 ppm) and Vanadium (50 ppm).

Copper: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Ferrous sulfate heptahydrate (0083)

Chromium, Copper, Nickel: in line with the Ph. Eur. Implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the current limits. In addition, the following impurity will be added: Cobalt (25 ppm).

Flurbiprofen (1519)

Identification: the 2nd identification series deleted, as the substance is not used in common or hospital pharmacies.

Related substances: specifications updated to reflect the current quality of substances in approved medicinal products on the market; an explicit criterion for unspecified impurities introduced in accordance with the general monograph *Substances for pharmaceutical use (2034)*.

Impurities: transparency list updated.

Fosinopril sodium (1751)

Related substances: specifications updated to reflect the current quality of substances in approved medicinal products on the European market.

Assay: volumetric titration in aqueous medium replaced by a new more robust non aqueous titration method.

Human albumin solution (0255)

Molecular-size distribution: the monograph was revised to reflect analytical improvement by:

- adjusting the sample preparation, chromatographic parameters and test conditions;
- deleting the use of sodium azide (classified as a CMR) as preservative in the mobile phase described in the monograph;
- including tools for peak identification and assessment of system suitability;
- amending the acceptance criterion.

Further amendments were made, in line with the Technical guide for the elaboration of monographs 7th Edition (2015).

Hydralazine hydrochloride (0829)

Identification: former test A deleted since the performance of UV-Vis tests is deemed unfeasible for pharmacies; description of sample preparation deleted from former test B; former test E modified.

Impurity B: TLC method replaced by new LC method.

Related substances: new LC method introduced covering 3 new impurities.

Impurities: section added.

Hydroxyethylcellulose (0336)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Hydroxypropylcellulose (0337)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Hydroxypropylcellulose, low-substituted (2083)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Hypromellose (0348)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Irbesartan (2465)

Further to the CHMP* opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 regarding the detection, management and prevention of presence of *N*-nitrosamines in medicinal products for human use (see assessment report published on 25 June 2020**) and the CHMP* decision to apply these recommendations to “sartans medicinal products” (see news published on 13 November 2020***), a revised version of this monograph is proposed for adoption as a minor revision and publication in Supplement 10.6 to align the Ph. Eur. requirements with the latest regulatory decisions.

Production: section completely reworded; recommendation to perform a risk assessment of the manufacturing process and, if needed, implement a control strategy for the detection and control of *N*-nitrosamine impurities added.

Tests: Nitrosamines test deleted.

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Lacosamide tablets (2989)

Dissolution. Test revised to bring it in line with the new policy.

Losartan potassium (2232)

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Production: section completely reworded; recommendation to perform a risk assessment of the manufacturing process and, if needed, implement a control strategy for the detection and control of *N*-nitrosamine impurities added.

Tests: Nitrosamines test deleted.

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Magnesium carbonate, light (0042)

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limit. In addition, the following impurities will be added: Cobalt (1 ppm), Nickel (50 ppm) and Vanadium (5 ppm).

Magnesium stearate (0229)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Methyl parahydroxybenzoate (0409)

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Methylcellulose (0345)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Nitrofurantoin (1135)

Related substances: CRS strategy modified where the new nitrofurantoin for peak identification A CRS is used to identify only the peak due to impurity A; grade of water used in the mobile phase amended in accordance with Technical Guide (2015); identification of impurities section modified accordingly.

Olmесartan medoxomil (2600)

Further to the CHMP* opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 regarding the detection, management and prevention of presence of *N*-nitrosamines in medicinal products for human use (see assessment report published on 25 June 2020**) and the CHMP* decision to apply these recommendations to “sartans medicinal products” (see news published on 13 November 2020***), a revised version of this monograph is proposed for adoption as a minor revision and publication in Supplement 10.6 to align the Ph. Eur. requirements with the latest regulatory decisions.

Production: section completely reworded; recommendation to perform a risk assessment of the manufacturing process and, if needed, implement a control strategy for the detection and control of *N*-nitrosamine impurities added.

Tests: Nitrosamines test deleted.

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Oxybutynin hydrochloride (1354)

Related substances: addition of a new impurity; specifications widened based on batch data, acceptance criteria expressed quantitatively.

all-rac-Phytomenadione (3011)

Title, definition, nomenclature and structures: updated to reflect that the 4 possible stereoisomers of each of the cis/trans configurations are covered by the monograph.

Optical rotation: dioxan class 2 solvent replaced by trimethylpentane.

Impurity B: structure and nomenclature updated in the same way as the main substance.

Potassium metabisulfite (2075)

Selenium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Povidone (0685)

Functionality-related characteristics: white diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Pravastatin sodium (2059)

Related substances: in preparation of reference solution (a), volume expressed using fewer significant figures due to the qualitative use of this solution; reagent used to describe stationary phase modified; grades of solvents used in mobile phase amended in accordance with Technical Guide (2015).

Assay: description of calculation of percentage content modified; CRS name changed and conversion factor added.

Propyl parahydroxybenzoate (0431)

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A footnote has been included in the text to refer to chapter 5.8. Pharmacopoeial harmonisation. Non-harmonised attributes have been placed between black diamonds (◆ ◆), while local requirements only present in the Ph. Eur. text have been placed between white diamonds (◇ ◇).

Raltegravir chewable tablets (2939)

Dissolution. Test revised to bring it in line with the new policy.

Raltegravir tablets (2938)

Dissolution. Test revised to bring it in line with the new policy and additional requirements at levels 2 and 3 included.

Regorafenib tablets (3023)

Dissolution. Test revised to bring it in line with the new policy.

Riociguat tablets (3079)

Dissolution. Test revised to bring it in line with the new policy.

Rivaroxaban tablets (3021)

Dissolution. Test revised to bring it in line with the new policy.

Rosuvastatin calcium (2631)

Impurities: structure of impurity K revised; new unspecified impurity added to the transparency list.

Rosuvastatin tablets (3008)

Dissolution. Test revised to bring it in line with the new policy

Salbutamol sulfate (0687)

Related substances: reference solution (e) adapted to accommodate new CRS strategy for *salbutamol sulfate for system suitability CRS*.

Sertaconazole nitrate (1148)

Content: lower limit updated.

Identification: 2nd identification series deleted as substance not used in pharmacies and to avoid use of toxic reagents.

Related substances: specifications updated to reflect current quality of substances in approved medicinal products on the European market; explicit criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; grades of solvents amended in accordance with Technical guide (2015); system suitability criterion modified.

Impurities: transparency list updated.

Sitagliptin tablets (2927)

Disintegration. Test revised to bring it in line with the new policy.

Sodium calcium edetate (0231)

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Sodium starch glycolate (type A) (0983)

Functionality-related characteristics. White diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Sodium starch glycolate (type B) (0984)

Functionality-related characteristics. White diamonds have been added to clarify that this section, which is non-mandatory, is only present in the Ph. Eur. text and not subject to pharmacopoeial harmonisation.

Sodium stearate (2058)

Nickel: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Sodium sulfite (0775)

Selenium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Sodium sulfite heptahydrate (0776)

Selenium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.

Sorafenib tablets (3022)

Dissolution. Test revised to bring it in line with the new policy.

Talc (0438)

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Terazosin hydrochloride dihydrate (2021)

Related substances: new more robust method introduced to control all impurities.

Impurities N and O: tests deleted as impurities N and O are now controlled by the method for related substances.

Ticagrelor tablets (3097)

Dissolution. Test revised to bring it in line with the new policy.

Tigecycline (2825)

Related substances: despite non being toxic, when present above 0.02 per cent, impurity D gives an undesirable colour to the substance that makes it unsuitable for use in a medicinal product. A limit test for impurity D using the method for related substances as initially published in Pharmeuropa 28.2 has been introduced.

Tobramycin (0645)

Identification A, B: *tobramycin for identification CRS* introduced to replace *tobramycin CRS* in these tests.

Related substances: preparation of reference solution (a) adjusted to take into account the presentation of *tobramycin CRS* as a lyophilised material.

RRR- α -Tocopheryl hydrogen succinate (1259)

Absorbance: update of the current range for the specific absorbance at 284 nm based on current batch data.

Valsartan (2423)

Further to the CHMP* opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 regarding the detection, management and prevention of presence of *N*-nitrosamines in medicinal products for human use (see assessment report published on 25 June 2020**) and the CHMP* decision to apply these recommendations to “sartans medicinal products” (see news published on 13 November 2020***), a revised version of this monograph is proposed for adoption as a minor revision and publication in Supplement 10.6 to align the Ph. Eur. requirements with the latest regulatory decisions.

Production: section completely reworded; recommendation to perform a risk assessment of the manufacturing process and, if needed, implement a control strategy for the detection and control of *N*-nitrosamine impurities added.

Tests: Nitrosamines test deleted.

CHMP* : Committee for Human Medicinal Products of the European Medicines Agency

** https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf

*** <https://www.ema.europa.eu/en/news/nitrosamines-ema-aligns-recommendations-sartans-those-other-medicines>

Verapamil hydrochloride (0573)

Identification: test modified in order to avoid the use of potassium dichromate (REACH reagent).

Related substances: last step of the gradient extended to ensure elution of impurity M; the value for the resolution adjusted.

Wheat starch (0359)

Total protein. Revised to clarify the procedure.

Zinc acetate dihydrate (1482)

Cadmium, Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limits.

Arsenic, Copper: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests are deleted.

Zinc gluconate (2164)

Cadmium: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limit. In addition, the following impurities will be added: Lead (2 ppm) and Thallium (2 ppm).

Zinc oxide (0252)

Cadmium, Lead: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test will be kept with the updated limits. In addition, the following impurity will be added: Thallium (5 ppm).

Arsenic: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test is deleted.