Comments concerning revised texts published in Supplement 10.8

The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the June session and published in Supplement 10.8.

When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.8. 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

2.5.3. Hydroxyl value

Method A: the type of condenser has been modified to take into account current practices. The words ", noting the volume added" have been deleted, because the volume referred to (*pyridine R*) is not used in any calculation.

2.9.12. Sieve test

The classification of powders according to their degree of fineness is covered by the harmonised general chapter *2.9.35. Powder fineness*.

5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include 1 new monograph published in Supplement 10.8.

GENERAL MONOGRAPHS

Chemical precursors for radiopharmaceutical preparations (2902)

Bacterial endotoxins: limit widened from "maximum 100 IU per gram" to "maximum 1 IU/mg" to take account of small quantities used, small batch sizes produced and analytical limitations.

DOSAGE FORMS

Rectal preparations (1145)

Production: control of particle size moved to general production section and deleted from individual production sections.

Tests:

- Uniformity of dosage units: applies to liquid or semi-solid preparations supplied in single-dose containers only if intended for a systemic effect. The test remains a requirement for all solid single-dose rectal preparations (intended either for a systemic or local effect).

- Uniformity of content: if the test for uniformity of content is applied, only compliance with Test B is required. Test B is considered justified as these are low-risk preparations.

- Dissolution: switched to general requirement, unless otherwise justified and authorised; wording aligned with that of other monographs, such as Tablets (0478); release test removed from individual production sections.

Definitions: aligned with Standard Terms, where possible.

Tablets for rectal solutions or suspensions: compliance with the monograph *Tablets (0478)* added.

VACCINES FOR HUMAN USE

Diphtheria and tetanus vaccine (adsorbed) (0444)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria and tetanus vaccine (adsorbed, reduced antigen(s) content) (0647)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus and hepatitis B (rDNA) vaccine (adsorbed) (2062)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed) (1931)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) (2764)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus and pertussis (whole cell) vaccine (adsorbed) (0445)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (2328)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (acellular, component) and haemophilus type b conjugate vaccine (adsorbed) (1932)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (acellular, component) and hepatitis B (rDNA) vaccine (adsorbed) (1933)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed) (1934)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (2329)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2067)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2065)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (whole cell) and poliomyelitis (inactivated) vaccine (adsorbed) (2061)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria, tetanus, pertussis (whole cell), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2066)

Specific toxicity of the diphtheria component: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the purified diphtheria toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Diphtheria vaccine (adsorbed) (0443)

Specific toxicity: test deleted. The requirement to perform the test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the bulk purified toxoid.

Diphtheria vaccine (adsorbed, reduced antigen content) (0646)

Specific toxicity: test deleted. The requirement to perform the Test for specific toxicity on the product as part of validation of the production process is considered redundant because a more sensitive test for residual toxin is performed routinely on the bulk purified toxoid (in accordance with the monograph on *Diphtheria vaccine (adsorbed) (0443)*).

Influenza vaccine (split virion, inactivated) (0158)

Total protein: limit for total protein per dose removed to accommodate quadrivalent influenza vaccines (the original monograph was established for trivalent vaccines). A sentence was also added to cover the case of high-dose influenza vaccines with higher total protein contents.

Editorial changes have also been made throughout the monograph.

Influenza vaccine (surface antigen, inactivated) (0869)

Total protein: limit for total protein per dose removed to accommodate quadrivalent influenza vaccines (the original monograph was established for trivalent vaccines).

Editorial changes have also been made throughout the monograph.

Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) (2149)

Total protein: limit revised to take into account the current specification for the corresponding quadrivalent influenza vaccine available on the European market.

Editorial changes have also been made throughout the monograph.

VACCINES FOR VETERINARY USE

Clostridium novyi (type B) vaccine for veterinary use (0362)

A European Initiative for Inter-laboratory study aiming at validating Vero cell-based alternatives to the mouse tests currently in use for in-process quality control of Clostridium septicum vaccines (BSP130*) lead to the revision of the monograph on C*lostridium septicum vaccine for veterinary use (0364)*. Like Clostridium septicum, Clostridium novyi is a cytotoxic Clostridium. The conclusions drawn for Clostridium septicum in BSP130 should therefore also be valid for Clostridium novyi. In light of these results, the long-term aim is to replace tests on mice with *in vitro* tests, for example on cells, for all these vaccines.

As a result, the Minimum Lethal Dose (MLD) and Total Combining Power (TCP) assays using mice as indicator of toxicity are replaced by a suitable *in vitro* method (e.g. in Vero cells).

Residual toxicity (section 2-3-1). In the interests of animal welfare and further to the BSP130 study, the use of a suitable test method (preferably *in vitro* e.g. in suitable cell cultures as indicator of toxicity instead of mice) has been introduced in the monograph. This is to encourage manufacturers to develop *in vitro* methods.

Antigen content (section 2-3-2). A test for antigen content has been added, since the test is regularly performed by the manufacturer; the test contributes to consistency of production. Further to the BSP130 study, manufacturers are encouraged to develop *in vitro* methods. It has to be noted that the TCP is a functional test, which is an advantage compared to an ELISA or an immunological test, and can be done *in vitro*, using suitable cell cultures as indicator of toxicity instead of mice.

Batch potency test (section 2-3-3). It has become apparent, that several *in vitro* methods are available for the second phase of the batch potency test (determination of antibodies in the serum of vaccinated rabbits). In the interests of animal welfare the wording has been amended to favour the use of *in vitro* methods. In addition, the mention that the homologous reference serum against C. novyi alpha antitoxin should be calibrated in International Units has been deleted.

Identification (section 3-1). A suitable test to prove that the vaccine contains the toxoid of the Clostridium strain as stated under Definition must be carried out. In the interests of animal welfare, the identity test in animals has been deleted although it can still be used if no validated alternative method is available. This should encourage manufacturers to develop alternative methods.

Residual toxicity (formerly section 3-3). Deleted from tests on final product because no reversion to toxicity has ever been reported. Furthermore, this is in line with the general monograph *Vaccines for veterinary use (0062)* stating the conditions under which the residual toxicity test may be omitted on the final bulk and the final batch.

* See https://pharmeuropa.edqm.eu/app/BioSN/content/BioSN/Bio_SciNotes_2020.pdf and https://pharmeuropa.edqm.eu/app/BioSN/content/BioSN-0/2021-5-Clostridium-septicum-vaccine-antigens-Part-2.pdf

Clostridium perfringens vaccine for veterinary use (0363)

A European Initiative for Inter-laboratory study aiming at validating Vero cell-based alternatives to the mouse tests currently in use for in-process quality control of Clostridium septicum vaccines (BSP130*) lead to the revision of the monograph on *Clostridium septicum vaccine for veterinary use (0364)*. Like Clostridium septicum, Clostridium perfringens is a cytotoxic Clostridium. The conclusions drawn for Clostridium septicum in BSP130 should therefore also be valid for Clostridium perfringens. In light of these results, the long-term aim is to replace tests on mice with *in vitro* tests, for example on cells, for all these vaccines.

As a result, the Minimum Lethal Dose (MLD) and Total Combining Power (TCP) assays using mice as indicator of toxicity are replaced by a suitable *in vitro* method (e.g. in Vero cells).

Residual toxicity (section 2-3-1). In the interests of animal welfare and further to the BSP130 study, the use of a suitable test method (preferably *in vitro* e.g. in suitable cell cultures as indicator of toxicity instead of mice) has been introduced in the monograph. This is to encourage manufacturers to develop *in vitro* methods.

Antigen content (section 2-3-2). A test for antigen content has been added, since the test is regularly performed by the manufacturer; the test contributes to consistency of production. Further to the BSP130 study, manufacturers are encouraged to develop *in vitro* methods. It has to be noted that the TCP is a functional test, which is an advantage compared to an ELISA or an immunological test, and can be done *in vitro*, using suitable cell cultures as indicator of toxicity instead of mice.

Batch potency test (section 2-3-3). It has become apparent that several *in vitro* methods are available for the second phase of the batch potency test (determination of antibodies in

the serum of vaccinated rabbits). In the interests of animal welfare, the wording has been amended to favour the use of *in vitro* methods. In addition, the mention that the homologous reference serum against C. perfringens antitoxin should be calibrated in International Units has been deleted.

Identification (section 3-1). A suitable test to prove that the vaccine contains the toxoid of the Clostridium strain as stated under Definition must be carried out. In the interests of animal welfare, the identity test in animals has been deleted although it can still be used if no validated alternative method is available. This should encourage manufacturers to develop alternative methods.

Residual toxicity (formerly section 3-3). Deleted from tests on the final product because no reversion to toxicity has ever been reported. Furthermore, this is in line with the general monograph *Vaccines for veterinary use (0062)* stating the conditions under which the residual toxicity test may be omitted on the final bulk and the final batch.

* See https://pharmeuropa.edqm.eu/app/BioSN/content/BioSN/Bio_Sci_Notes_2020.pdf and https://pharmeuropa.edqm.eu/app/BioSN/content/BioSN-0/2021-5-Clostridium-septicum-vaccine-antigens-Part-2.pdf

Clostridium septicum vaccine for veterinary use (0364)

In the interest of animal welfare and further to a European Initiative for Inter-laboratory study aiming at validating Vero cell-based alternatives to the mouse tests currently in use for in-process quality control of Clostridium septicum vaccines (BSP130*), this monograph has been revised to replace the Minimum Lethal Dose (MLD) and Total Combining Power (TCP) assays in mice by *in vitro* tests in tissue culture (e.g. in Vero cells).

Residual toxicity (section 2-3-1). The replacement of the method using mice as indicator of toxicity by a suitable *in vitro* method (e.g. in Vero cells) has been introduced in the monograph.

Antigen content (section 2-3-2). A test for antigen content has been added, since the test is regularly performed by the manufacturer; the test contributes to consistency of production. It has to be noted that the TCP is a functional test, which is an advantage compared to an ELISA or an immunological test, and can be done *in vitro*, using suitable cell cultures as indicator of toxicity instead of mice.

Batch potency test (section 2-3-3). It has become apparent, that several *in vitro* methods are available for the second phase of the batch potency test (determination of antibodies in the serum of vaccinated rabbits). In the interest of animal welfare the wording has been amended to favour the use of *in vitro* methods. In addition, the mention that the homologous reference serum against C. septicum antitoxin should be calibrated in International Units has been deleted.

Identification (section 3-1). A suitable test to prove that the vaccine contains the toxoid of the Clostridium strain as stated under Definition must be carried out. In the interests of animal welfare, the identity test in animals has been deleted although it can still be used if no validated alternative method is available. This should encourage manufacturers to develop alternative methods.

Residual toxicity (formerly section 3-3). Deleted from tests on the final product because no reversion to toxicity has ever been reported. Furthermore, this is in line with the general monograph *Vaccines for veterinary use (0062)* stating the conditions under which the residual toxicity test may be omitted on the final bulk and the final batch.

* See https://pharmeuropa.edqm.eu/app/BioSN/content/BioSN/Bio_Sci_Notes_2020.pdf and https://pharmeuropa.edqm.eu/app/BioSN/content/BioSN-0/2021-5-Clostridium-septicum-vaccine-antigens-Part-2.pdf

RADIOPHARMACEUTICAL PREPARATIONS AND STARTING MATERIALS FOR RADIOPHARMACEUTICAL PREPARATIONS

Betiatide for radiopharmaceutical preparations (2551)

Water: replacement of semi-micro determination of water (*2.5.12*) by micro determination of water (*2.5.32*) due to the small amount of water expected and the small batch sizes produced.

Copper tetramibi tetrafluoroborate for radiopharmaceutical preparations (2547)

pH: test deleted as not needed to guarantee the quality of the substance.

Fluoroethyl-L-tyrosine (^{18}F) injection (2466)

Impurity B (tetrabutylammonium): LC test replaced by TLC test given in general method (*2.4.33*) which is a faster and more reliable TLC procedure.

Enantiomeric purity: test renamed “Impurities C and D” and replaced by a faster and more reliable TLC procedure.

Impurity D ([^{18}F]fluoride): test deleted, as the new test for Impurities C and D also controls [^{18}F]fluoride (impurity D).

Sodium molybdate (^{99}Mo) solution (fission) (1923)

Production/Radionuclidic purity: to limit the risk of proliferation of highly enriched uranium and in view of the potential shortage, alternative ways of producing sodium molybdate (^{99}Mo) solution using low enriched uranium have been established. A possible radionuclidic impurity seen in the use of low enriched uranium is tungsten-187. This impurity is difficult to control in the final article and is thus controlled during the production process.

Technetium (^{99m}Tc) macrosalb injection (0296)

Definition: transfer of the part of the definition section relating to Sodium pertechnetate (^{99m}Tc) injection and Human albumin solution to the Production section to underline that the quality of Sodium pertechnetate (^{99m}Tc) injection and Human albumin solution needs to be ensured.

Production/Physiological distribution: transfer of the physiological distribution test from the Tests section to the Production section, considering that the particle size test is an indicator for the consistency of production and thus for the physiological distribution. The physiological distribution test then no longer consists of a routine test, resulting in a considerable reduction of animal tests.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Arnica flower (1391)

Identification/test: TLC replaced with HPTLC (general chapter *2.8.25*); the species Arnica chamissonis Less. added to the test for foreign matter.

Assay: sample preparation improved to avoid the presence of interfering flavonoids in the test solution, and test to verify the absence of interfering flavonoids included.

Arnica tincture (1809)

Identification/Tests: TLC replaced by high-performance thin-layer chromatography (HPTLC) in accordance with chapter *2.8.25* and test on Arnica chamissonis Less. introduced.

Assay: sample preparation improved to avoid the presence of interfering flavonoids in the test solution, and test to verify the absence of interfering flavonoids included.

Mullein flower (1853)

Definition: revised to cover hybrids and mixtures.

Identification: identification tests A, B and C updated to take into account the changes to the definition; in identification test C, TLC replaced by HPTLC in line with chapter *2.8.25*.

Saw palmetto fruit (1848)

To improve handling of the herbal drug the powdering procedure has been detailed.

HOMOEOPATHIC PREPARATIONS

Methods of preparation of homoeopathic stocks and potentisation (2371)

Methods 1.5.1 and 1.5.2: 2 new homoeopathic manufacturing methods have been introduced for mother tinctures prepared by fermentation (rhythmic conditions); these methods have been adapted from the German Homoeopathic Pharmacopoeia (Homöopathisches Arzneibuch, HAB), and the equivalent HAB method numbers and titles are given for convenience.

Moreover, the monograph has been slightly revised for overall consistency such as:

- the test sample is specified for the determination of the loss on drying and the water content;

- information relating to maceration that was in the introduction has been moved to the section 1.1 on mother tinctures.

MONOGRAPHS

Air, medicinal (1238)

Nitrogen monoxide and nitrogen dioxide: modification of the description of reference gas (b).

Ascorbic acid (0253)

Iron: reference to Method I deleted as both methods described in general chapter *2.2.23* are suitable for the determination.

Botulinum toxin type A for injection (2113)

Specific activity (bulk purified toxin), Assay (final lot). Information on alternative *in vitro* methods for potency updated to reflect the current situation for authorised products. The possibility to use a cell-based assay is specifically mentioned as an alternative to the LD_{50} assay.

Assay. Introduction of a new section on the application of humane end-points in the LD_{50} assay, to reduce animal suffering.

Bromazepam (0879)

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; system suitability criterion amended.

Loss on drying: conditions aligned with the general chapter *2.2.32*.

Calcium gluconate for injection (0979)

Oxalates: new ion chromatography method has been introduced.

Cholecalciferol concentrate (powder form) (0574)

Identification: as in the monograph for *Cholecalciferol concentrate (oily form) (0575)* the second identification has been deleted. The TLC that required the use of ether has been deleted and replaced by a UV identification test that refers to the UV spectra obtained from the respective peaks obtained in the LC-assay.

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

Cod-liver oil (1192)

Title: title modified to delete the reference of ‘type A’.

Vitamin D3: reagent used to describe stationary phase modified.

Composition of fatty acids: the mention of ‘type A’ is deleted in Figure 1192.-1.

Domperidone (1009)

Identification: 2nd identification series deleted, as the substance is not used in pharmacies; melting point deleted as IR alone was found sufficient for discrimination.

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

Domperidone maleate (1008)

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

Related substances: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market. Explicit criterion for unspecified impurities introduced; system suitability amended.

Dronedarone hydrochloride (3039)

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

Dydrogesterone (2357)

Specific optical rotation: test deleted as considered not relevant in view of recent data.

Related substances: impurities specifications updated based on recent batch data from approved manufacturer on the European market.

Fludarabine phosphate (1781)

Related substances, test A: chromatogram provided with *fludarabine for peak identification CRS* to allow a better identification of imp C.

Folic acid hydrate (0067)

Related substances: pH of mobile phase adjusted to 6.4 to ensure reproducible separation.

Glycerol (0496)

Sugars: the preparation of the carbonate-free solution of sodium hydroxide has been simplified.

Glycerol (85 per cent) (0497)

Sugars: the preparation of the carbonate-free solution of sodium hydroxide has been simplified.

Human normal immunoglobulin for intramuscular administration (0338)

Molecular-size distribution: addition of:

- an instruction to use the normalisation procedure;

- information on the identification of the fragments peaks.

Human normal immunoglobulin for intravenous administration (0918)

Molecular-size distribution: addition of:

- an instruction to use the normalisation procedure;

- information on the identification of the fragments peaks.

Human normal immunoglobulin for subcutaneous administration (2788)

Molecular-size distribution: addition of:

- an instruction to use the normalisation procedure;

- information on the identification of the fragments peaks.

Hydrochloric acid, concentrated (0002)

Identification B: reaction (b) deleted to avoid the use of toxic reagent.

Residue on evaporation: use of rotary evaporator added as an alternative to the current method.

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

Hydrochloric acid, dilute (0003)

Identification B: reaction (b) deleted to avoid the use of toxic reagent.

Residue on evaporation: use of rotary evaporator added as an alternative to the current method.

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

Manganese sulfate monohydrate (1543)

Iron, Zinc: the test will be kept with the current limits and a certain degree of flexibility in the choice of method to be used has been allowed.

Mebeverine hydrochloride (2097)

Chlorides: information has been added to the test to facilitate its application.

Assay: titration with sodium hydroxide.

Piperacillin sodium (1168)

Related substances: based on batch data, impurity G, previously qualified as other detectable impurity, has been specified to a limit of maximum 1.5 per cent and the limit of impurity S has been enlarged from 0.2 to 0.5 per cent***.***

Impurities: the status of impurity G has been updated***.***

Podophyllotoxin (2750)

Storage: data provided show that the substance is stable and that there is no need to store it at 2° C to 8° C.

Protamine sulfate (0569)

Related substances: revision of the number of significant figures in the reporting threshold (from 0.5 per cent to 0.50 per cent).

Sodium ascorbate (1791)

Iron: reference to Method I deleted as both methods described in general chapter *2.2.23* are suitable for the determination.

Spectinomycin dihydrochloride pentahydrate (1152)

Related substances: reagent used to describe stationary phase modified.

Assay: section aligned with the requirement prescribed in the definition section (calculation of the percentage content of (4*R*)-dihydrospectinomycin dihydrochloride from the sum of the contents of spectinomycin dihydrochloride and (4*R*)-dihydrospectinomycin dihydrochloride as both components have similar responses).

Spectinomycin sulfate tetrahydrate for veterinary use (1658)

Related substances: reagent used to describe stationary phase modified.

Assay: section aligned with the requirement prescribed in the definition section (calculation of the percentage content of (4*R*)-dihydrospectinomycin sulfate from the sum of the contents of spectinomycin sulfate and (4*R*)-dihydrospectinomycin sulfate as both components have similar responses).