

Comments Concerning Revised Texts Published in Supplement 7.2

Here follows information concerning technical modifications to revised texts adopted by the European Pharmacopoeia Commission at the June 2010 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

GENERAL TEXTS

2.4.23. Sterols in fatty oils

The chapter has been revised to allow the analyst to prepare the unsaponifiable matter as described in the corresponding test of the monographs and, consequently, to avoid the preparation of unsaponifiable matter twice, sometimes according to 2 different methods, one aiming at the determination of the unsaponifiable matter content and the other at isolating the sterols from the oil. In addition, this revision permits a more accurate separation of the sterol fraction using an LC method instead of the TLC one, as well as a faster separation of the sterols using a GC method.

2.6.20. Anti-A and anti-B haemagglutinins

A collaborative study was performed under the aegis of the Biological Standardisation Programme (BSP089) (published article: 'International collaborative study to evaluate candidate reference reagents to standardize haemagglutination testing for anti-A and anti-B in normal intravenous immunoglobulin products' in *Vox Sanguinis* 2009;97(2):160-68 supplemented by an article on the same subject published in *Pharmeuropa Bio & Scientific Notes* 2010(1):39-50). The study aimed at validating a direct haemagglutination method, using papain-treated cells, as a reference method for the screening of anti-A and anti-B antibodies in human normal immunoglobulin products and at establishing 3 BRPs, whose aims would be to standardise and control haemagglutination testing for anti-A and anti-B antibodies in human normal immunoglobulin products.

The monographs *Human normal immunoglobulin (0338)* and *Human normal immunoglobulin for intravenous administration (0918)* currently include a requirement to limit the level of anti-A and anti-B haemagglutinins, which was determined using the indirect anti-globulin test, described in chapter 2.6.20.

Further to the conclusive outcome of the collaborative study, the indirect method was replaced by the direct method in these monographs.

Consequently, chapter 2.6.20 has been revised to include the direct method as an additional method for the screening of anti-A and anti-B haemagglutinins.

It is noted that a similar collaborative study was organised several years ago for the screening of anti-D antibodies in human immunoglobulin; the direct haemagglutination method is already published in the Ph. Eur. in chapter 2.6.26. Test for anti-D antibodies in human immunoglobulin.

Reference preparations: the direct method requires the use of 3 BRPs: a positive control, a negative control and a limit test reference preparation. It is noted that the limit test reference preparation must only be used for clarifying borderline preparations, which give a titre greater than the titre of the positive control BRP (with preparations titrated from 25 g/L).

Method B (Interpretation of results): examples of interpretation of results are given (Figure 2.6.20.-1) for information in the Knowledge database.

2.6.26. Test for anti-D antibodies in human immunoglobulin

Chapter 2.6.20. *Anti-A and anti-B haemagglutinins* has been revised to include a direct haemagglutination method (see revision in this supplement). Elaboration of the direct method has been based on chapter 2.6.26 since both methods follow the same principle and methodology. Improvements introduced to the methodology for the direct method have also been introduced to chapter 2.6.26.

2.7.7. Assay of pertussis vaccine (whole cell)

Title: title modified to clarify scope of method and to use the same style as already implemented in chapter 2.7.16. *Assay of pertussis vaccine (acellular).*

GENERAL MONOGRAPHS

Vaccines for veterinary use (0062)

Minor use: a sentence has been added in the introduction to take into account the guideline EMA/CVMP/IWP/123243/2006, which offers a reduced set of requirements for the licensing of immunological veterinary medicinal products for which the use will be 'minor', i.e., the market will be limited either because the product involved is directed against the causal agent of a 'minor' disease or because the product is destined for a 'minor' species; the introduction of this provision in the Ph. Eur. allows licensing authorities to apply this guideline when necessary; a link to this guideline has been added in the Knowledge database.

Sterility: reference to specific monographs has been deleted since the general monograph applies to all

vaccines, including those that are not covered by a specific monograph; the particular case of live bacterial or fungal vaccines has been added.

Mycoplasma: reference to specific monographs has been deleted for the same reasons given for Sterility; it has been clarified that this test has to be carried out for all live viral vaccines.

Expiry date: a statement on the calculation of the expiry date has been added for veterinary vaccines.

Labelling: antigenic components have been included because it is necessary in some cases to mention them in addition to the type of bacteria used to produce the vaccine.

VACCINES FOR HUMAN USE

Hepatitis B vaccine (rDNA) (1056) Human papillomavirus vaccine (rDNA) (2441)

The monographs have been revised to take into account vaccines formulated with the adjuvant 3-*O*-desacyl-4'-

monophosphoryl lipid A; the revision should be read in conjunction with the monograph 3-*O*-Desacyl-4'-monophosphoryl lipid A (2537) covering 3-*O*-desacyl-4'-monophosphoryl lipid A up to the liquid bulk stage.

HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

Black horehound (1858) Digitalis leaf (0117)

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

Juniper (1532)

Assay: preparation of test sample described more precisely to improve reproducibility.

Mallow leaf (2391)

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

HOMOEOPATHIC PREPARATIONS

Homoeopathic preparations (1038)

Manufacturing methods: the text has been revised in order to reflect that the competent authority has the right to accept or reject particular combinations of manufacturing method and substance.

MONOGRAPHS

N-Acetyltirosine (1384)

Related substances: TLC replaced by LC in accordance with current policy; impurity B never found in any tested samples, therefore mentioned as other detectable impurity; wording for determination of total impurities modified: total now only expressed as percentage.

Ammonium: method updated and harmonised with other amino acid monographs.

Pyrogens: replaced by test for bacterial endotoxins.

Alfacalcidol (1286)

Related substances: relative retentions of specified impurities A, B and C added.

Arachis oil, refined (0263)

Composition of fatty acids: limits for palmitic, linoleic and eicosenoic acid revised to better correspond to results obtained with current production batches.

Benperidol (1172)

Related substances: explicit acceptance criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities introduced.

Betaxolol hydrochloride (1072)

Related substances: *betaxolol impurity C CRS*, *betaxolol for peak identification CRS* and relative retentions of specified impurities introduced for peak identification; explicit acceptance criterion introduced for unspecified impurities; disregard limit increased to 0.05 per cent.

Botulinum toxin type A for injection (2113)

Potency: introduction of a paragraph stressing the importance of using alternative methods (after validation with respect to the LD50 assay) that are preferable in terms of animal welfare. In the previous text the alternative methods were enumerated (1-3), which could give the impression that there was an order of preference for the alternative methods and also that the given list was exhaustive. Therefore, the examples of alternative methods are now mentioned in one sentence. Also, cell-based assays have been added among the examples.

More information on the alternative methods mentioned in the monograph and in particular on the mouse local paralysis assay can be found in the following publications:

- Jones RG, Alsop TA, Hull R *et al.* Botulinum type A toxin neutralisation by specific IgG and its fragments: a comparison of mouse systemic toxicity and local flaccid paralysis assays. *Toxicon* 2006;**48**(3):246-54.
- Sesardic D, Jones RG, Leung T *et al.* Detection of antibodies against botulinum toxins. *Mov Disord* 2004;**19**(Suppl 8):S85-91.

Bromperidol (1178)**Bromperidol decanoate (1397)**

Related substances: explicit acceptance criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities introduced.

Buserelin (1077)

Identification: tests A and B or tests A and C may alternatively be carried out, in accordance with current policy.

Identification B: test revised in line with general chapter 2.2.64. *Peptide identification by nuclear magnetic resonance spectrometry.*

Identification C: the methods to be used for hydrolysis and analysis in the amino acid analysis are presented in a more flexible manner since this test is prescribed for identification purposes; statement concerning tryptophan deleted as this amino acid is destroyed by acid hydrolysis.

Labelling: introduction of a statement on the suitability of the substance for use in the manufacture of parenteral preparations, in accordance with current policy.

Butyl parahydroxybenzoate (0881)

Revision agreed by the PDG (Pharmacopoeial Discussion Group) within the framework of international harmonisation.

Identification: identification D deleted.

Related substances: TLC replaced by LC.

Assay: titration replaced by the LC used in the test for related substances.

Impurities: other detectable impurity E added.

Cefepime dihydrochloride monohydrate (2126)

Related substances: following degradation of impurity E in *cefepime dihydrochloride monohydrate for system suitability CRS*, impurity E has been introduced as a single CRS in a separate reference solution (reference solution (d)).

Cinnarizine (0816)

Related substances: explicit acceptance criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities introduced.

Copovidone (0891)

Definition: CAS number added.

Solution S: more precise concentration described for the solution.

Hydrazine: development expressed in new style.

Functionality-related characteristics: a section has been added; italicised paragraph modified to take account of possible cross-references to tests present in the mandatory part of the monograph. Copovidone is mainly used as binder for dry granulation in tablets and granules; viscosity, particle-size distribution and bulk and tapped density are

therefore included. It may also be used as film former in coated dosage forms or aerosols; viscosity is therefore included.

Cyproterone acetate (1094)

Related substances: limits for impurities B, C, E and G increased, based on current batch data; transparency list updated.

Dimeticone (0138)

Functionality-related characteristics: a section has been added; italicised paragraph modified to take account of possible cross-references to tests present in the mandatory part of the monograph.

Dimeticone is used as antifoaming agent and as emollient in oil-in-water emulsions, as substitute to paraffin or soft paraffin. The use as antifoaming agent being a minor one, it has been decided to focus on the use of dimeticone as emollient; a cross-reference to the test for viscosity is included.

Domperidone (1009)**Droperidol (1010)****Estriol (1203)**

Related substances: explicit acceptance criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities introduced.

Fluphenazine dihydrochloride (0904)

Related substances: update of LC method, in particular to allow control of 2 additional impurities.

Heavy metals: replacement of method C by method H.

Impurities: introduction of other detectable impurities E and F.

Haloperidol decanoate (1431)

Related substances: explicit acceptance criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities introduced.

Human normal immunoglobulin (0338)

Characters: appearance of liquid preparation revised.

Anti-A and anti-B haemagglutinins (2.6.20). Further to the conclusive outcome of a collaborative study that aimed at validating a direct haemagglutination method, using papain-treated cells, as a reference method for the screening of anti-A and anti-B antibodies in human normal immunoglobulin products, and at establishing 3 BRPs whose aims would be to standardise and control haemagglutination testing for anti-A and anti-B antibodies in human normal immunoglobulin products, the indirect method (method A) has been replaced by the direct method (method B) in this monograph (see revised chapter 2.6.20 published in Supplement 7.2 for details of the method).

The collaborative study 'International collaborative study to evaluate candidate reference reagents to standardize

haemagglutination testing for anti-A and anti-B in normal intravenous immunoglobulin products' is published in *Vox Sanguinis* 2009;**97**(2):160-68 and is supplemented by an article on the same subject in *Pharmeuropa Bio & Scientific Notes* 2010(1):39-50.

Human normal immunoglobulin for intravenous administration (0918)

Anti-A and anti-B haemagglutinins (2.6.20). Further to the conclusive outcome of a collaborative study that aimed at validating a direct haemagglutination method, using papain-treated cells, as a reference method for the screening of anti-A and anti-B antibodies in human normal immunoglobulin products, and at establishing 3 BRPs whose aims would be to standardise and control haemagglutination testing for anti-A and anti-B antibodies in human normal immunoglobulin products, the indirect method (method A) has been replaced by the direct method (method B) in this monograph (see revised chapter 2.6.20 published in Supplement 7.2 for details of the method).

The collaborative study 'International collaborative study to evaluate candidate reference reagents to standardize haemagglutination testing for anti-A and anti-B in normal intravenous immunoglobulin products' is published in *Vox Sanguinis* 2009;**97**(2):160-68 and is supplemented by an article on the same subject in *Pharmeuropa Bio & Scientific Notes* 2010(1):39-50.

Human tetanus immunoglobulin (0398)

A collaborative study was performed under the aegis of the Biological Standardisation Programme (BSP079) (article published in *Pharmeuropa Bio & Scientific Notes* 2009(1):11-25: 'Collaborative study for the validation of alternative *in vitro* potency assays for human tetanus immunoglobulin'), which aimed at validating and comparing 2 *in vitro* assays, i.e., an enzyme-linked immunoassay (EIA) and a toxoid inhibition assay (TIA). This project, which is in line with the 3Rs concept, was run to further promote the replacement of animal testing. Both methods were shown to be comparable in terms of precision (repeatability and reproducibility). Furthermore, they were able to discriminate between the low-, medium- and high-potency products. The study also showed a good correlation between EIA and TIA potency results as well as close agreement between *in vivo* and *in vitro* values. Further to the conclusive outcome of the study, the monograph has been revised to add the 2 methods.

Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30 per cent (1129)

Characters: sensitivity to microbial contaminants is normally not stated; the reference has therefore been deleted.

Apparent viscosity: depending on whether a product shows Newtonian or non-Newtonian behaviour and depending on the apparatus used (2.2.9: capillary viscometer; 2.2.10: concentric cylinder viscometer or cone-plate viscometer), the measured value is a value of apparent viscosity or of true viscosity; the title has thus been changed to the generic term 'Viscosity'.

Storage: self-evident information deleted.

Labelling: this information is already given in the monograph *Substances for pharmaceutical use (2034)* and has therefore been deleted.

Functionality-related characteristics: a section has been added; italicised paragraph modified to take account of possible cross-references to tests present in the mandatory part of the monograph.

This excipient is used as a gastro-resistant coating agent. Its viscosity must be low to allow spraying of the coating solution; a cross-reference to the test for viscosity is therefore included. The solubility of the film in different pH conditions reflects the use of this excipient; a cross-reference to the test for appearance and a test for solubility of a film are therefore included.

Methacrylic acid – methyl methacrylate copolymer (1:1) (1127)

Methacrylic acid – methyl methacrylate copolymer (1:2) (1130)

Apparent viscosity: depending on whether a product shows Newtonian or non-Newtonian behaviour and depending on the apparatus used (2.2.9: capillary viscometer; 2.2.10: concentric cylinder viscometer or cone-plate viscometer), the measured value is a value of apparent viscosity or of true viscosity; the title has thus been changed to the generic term 'Viscosity'.

Functionality-related characteristics: a section has been added; italicised paragraph modified to take account of possible cross-references to tests present in the mandatory part of the monograph.

These excipients are used as gastro-resistant coating agents. Their viscosity must be low to allow spraying of the coating solution; a cross-reference to the test for viscosity is therefore included. The solubility of the film in different pH conditions reflects the use of these excipients; a cross-reference to the test for appearance of a film and a test for solubility of a film are therefore included.

Nicergoline (1998)

Identification: IR spectrum replaced by a CRS in accordance with current policy.

Related substances: new method allows improved detection of impurity D and covers additional impurities H, I and J; limits updated based on current batch data and in line with current policy; wording for determination of total of impurities modified: total now only expressed as a percentage.

Olive oil, refined (1456)

Olive oil, virgin (0518)

Sterols: monographs revised following revision of chapter 2.4.23. *Sterols in fatty oils* published in Supplement 7.2. The analyst may use the unsaponifiable matter obtained in the test for unsaponifiable matter of the monographs. Consequently, this avoids the preparation of unsaponifiable matter twice according to 2 different methods, one aiming at the determination of the unsaponifiable matter content and the other at isolating the sterols from the oil. In addition, this revision avoids the use of ether and permits a more accurate separation of the sterol fraction using an LC

method instead of the TLC one, as well as a faster separation of the sterols using a GC method.

Ondansetron hydrochloride dihydrate (2016)

Impurity B: introduction of retardation factors for information.

Related substances: limit of 0.2 per cent introduced for sum of impurities E and F and sum of impurities A and G as full separation of these impurity pairs may not always be achieved; other limits reviewed, particularly with introduction of general acceptance criterion for unspecified impurities in accordance with current policy; wording for determination of total of impurities modified: total now only expressed as a percentage; combination of reference solutions with individual CRSs introduced to identify impurities A, E, F and G even if they are only partially separated or coelute; resolution criterion between impurities E and F deleted.

Polyacrylate dispersion 30 per cent (0733)

Apparent viscosity: depending on whether a product shows Newtonian or non-Newtonian behaviour and depending on the apparatus used (2.2.9: capillary viscometer; 2.2.10: concentric cylinder viscometer or cone-plate viscometer), the measured value is a value of apparent viscosity or of true viscosity; the title has thus been changed to the generic term 'Viscosity'.

Storage: self-evident information deleted.

Labelling: this information is already given in the monograph *Substances for pharmaceutical use (2034)*, and has therefore been deleted.

Functionality-related characteristics: a section has been added; italicised paragraph modified to take account of possible cross-references to tests present in the mandatory part of the monograph.

This excipient is used as film former or as matrix former in prolonged-release dosage forms. Its viscosity must be low to allow spraying of the coating solution; a cross-reference to the test for viscosity is therefore included. The absence of solubility of the film in different pH conditions reflects the use of this excipient; a cross-reference to the test for appearance of a film and a test for solubility of a film is included.

Povidone (0685)

Solution S: more precise concentration described for the solution.

Hydrazine: development revised.

Assay: sample size given in usual style.

Functionality-related characteristics: a section has been added; italicised paragraph modified to take account of possible cross-references to tests present in the mandatory part of the monograph.

Povidone is used as solubiliser and stabiliser (povidone K 11-18) in liquid dosage forms; the molecular mass, determined by the Viscosity test, expressed as K-value, and the viscosity itself, are relevant characteristics to assess these uses. Povidone may also be used as binder (povidone K 24-33 and K 85-95) in solid dosage forms (mainly wet granulation

for tablets and granules); the molecular mass is again relevant. Particle-size determination and determination of the bulk and tapped density are not considered relevant since povidone is used as a solution at concentrations ranging from 1 per cent to 5 per cent.

Prednisolone (0353)

Content: limits revised due to change to LC method and based on recent results.

Identification: IR and LC from related substances test deemed sufficient for identification.

Specific optical rotation: dioxan replaced by less-toxic solvent ethanol (96 per cent); limits revised accordingly.

Related substances: new LC method introduced, also used for assay; limits updated based on current batch data.

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

Impurities: transparency list updated.

Ribavirin (2109)

Related substances: introduction of a more robust revised method allowing better separation of impurities; according to recent batch data, impurity A is the only specified impurity.

Salbutamol sulfate (0687)

Related substances: elution order of impurities corrected; system suitability criteria updated based on results obtained during establishment of CRSs; wording for determination of total of impurities modified: total now only expressed as a percentage.

Simeticone (1470)

Functionality-related characteristics: a section has been added; italicised paragraph modified to take account of possible cross-references to tests present in the mandatory part of the monograph.

Simeticone is mainly used as a defoaming agent. The amount used being very low, viscosity is not considered as a relevant characteristic. However, the test for defoaming activity, included under Tests, is relevant; a cross-reference to this test is included.

all-rac- α -Tocopherol (0692)

all-rac- α -Tocopheryl acetate (0439)

Assay: requirement for symmetry factor added, differing from default criteria as given in general chapter 2.2.46.

Torasemide, anhydrous (2132)

Related substances: new specified impurity E added; wording for explicit acceptance criterion for unspecified impurities now aligned with general monograph *Substances for pharmaceutical use (2034)*; system suitability criterion (S/N ratio) added.

Tretinoin (0693)

Impurities: list updated based on additional information.