

COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 5.3

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the November 2004 session. This information completes the modifications indicated by lines in the margin in the supplement. Hence, the information below is not necessarily exhaustive.

ANALYTICAL METHODS

2.2.10. Viscosity - Rotating viscometer method

The previous general chapter on the rotating viscometer dealt with instruments that gave an absolute measure of viscosity. Viscometers giving a relative measure of viscosity, such as the Brookfield type are however widely used in pharmaceutical analysis. The decision of the European Pharmacopoeia Commission to deal with functionality-related characteristics in monographs on excipients now requires that this type of viscometer should be described in the general chapter. The whole chapter has been revised in accordance.

2.4.14. Sulphated ash

The minor revision of this general method is a consequence of the recent sign-off of a revised version of the test by the Pharmacopoeial Discussion Group (PDG). The changes are minor clarifications of the text but it is important to keep the methods published by the Ph. Eur., JP and USP as close as possible textually so that the harmonisation status of the text is apparent.

The requirement for "ignition to constant mass" has been replaced by a requirement for a "difference between consecutive weighings not exceeding 0.5 mg". This is equivalent to the definition of "constant mass" given in the General Notices, but since the definition in the JP and USP is different, it is preferable to state the requirement explicitly rather than by convention.

2.9.17. Test for extractable volume of parenteral preparations

2 introductory paragraphs have been deleted so that harmonisation only concerns the method. A temperature of 20-25 °C (if the preparation has to be warmed then cooled before the test) is specified since this gives flexibility and there is no appreciable effect on the result. "Hypodermic" has been deleted in the description of the syringe since this is a non-essential detail. Pooling of a sufficient number of containers to obtain the required volume (40 per cent of the graduated volume of the cylinder) is allowed where the nominal volume is 2 ml or less.

DOSAGE FORMS

Eye preparations (1163)

The previous version of the monograph required semi-solid preparations to be packed in tubes with a content of not more than 5 g. It appears that marketing applications were granted for larger contents i.e. 10 g, without causing problems of microbial contamination.

As a consequence, it has been decided to enlarge the maximum content allowed.

To be consistent with the labelling requirements for eye drops and eye lotions, a maximum of 4 weeks after opening the container is prescribed for semi-solid preparations.

VACCINES FOR HUMAN USE

Influenza vaccine (split virion, inactivated) (0158) Influenza vaccine (surface antigen, inactivated) (0869) Influenza vaccine (whole virion, inactivated) (0159)

A limit for ovalbumin was introduced into the monographs on influenza vaccines in the early 1990s, and was set at 1 µg of ovalbumin per human dose. Experience with available vaccines and the technical possibilities of present methods for determining ovalbumin suggest that the general limit can be lowered to match the real quality level of products. Following consultation with manufacturers supplying the European market, it was proposed to lower the limit for ovalbumin to 100 ng of ovalbumin per human dose. But since this limit cannot be fulfilled by all manufacturers, it has been decided to keep the limit of 1 µg of ovalbumin per human dose and to add that the limit is in any case not more than the amount stated on the label. It is then requested to state the maximum amount of ovalbumin on the label. It is

intended to encourage all manufacturers to lower this limit and to revise the monographs accordingly in a few years time. Furthermore the test for viral inactivation has been renamed test for residual infectious virus to improve clarity.

Influenza vaccine (surface antigen, inactivated, virosome) (2053)

To take into account recent comments and to harmonise with other influenza vaccines, it has been decided to increase this limit to 1 µg of ovalbumin per human dose and to state the maximum amount of ovalbumin on the label. It is also intended to encourage all manufacturers to lower this limit and to revise the monographs accordingly in a few years time. Moreover, the test for viral inactivation has been renamed 'Test for residual infectious virus' as for other influenza vaccine monographs.

Poliomyelitis vaccine (oral) (0215)

This monograph has been revised following revision by WHO. The more significant changes are:

- addition of a section on reference materials;
- addition of simian cytomegalovirus testing on monkeys for production of seed material and on single harvest;
- introduction of MAPREC profile (i.e. percentage of mutant) to be established on seed material;
- addition of MAPREC consistency on each single harvest;
- addition of MAPREC assay on pooled harvest;
- introduction of the neurovirulence test in transgenic mice as an alternative on pooled harvest;
- addition of acceptance criteria for the reference preparation under Thermal stability and Assay.

The WHO MAPREC assay and the WHO transgenic mice test are described in standard operating procedures (SOP) available from WHO, Quality and Safety of Biologicals, Geneva. For practical reasons and to avoid unnecessary updates of the monograph, reference is made to the WHO SOPs in the monograph.

Tick-borne encephalitis vaccine (inactivated) (1375)

For vaccines where the seed virus has been passaged in mouse brains, at least 2 passages in cell culture between the master seed lot and the production cell culture are required to reduce carry over of substances originating from the mouse brain.

The use of alternative methods, notably *in vitro*, instead of intracerebral inoculation into mice in the inactivation test is allowed, and the use of an *in vitro* test is encouraged.

SUTURES FOR HUMAN USE**Sutures, sterile non-absorbable (0324)**

Depending on the source of the poly(vinylidene difluoride) sutures, minor differences in the IR spectrum

are apparent. Therefore the reference spectrum has been replaced by mention of the significant bands in the spectrum.

HOMOEOPATHIC PREPARATIONS**Common stinging nettle for homoeopathic preparations (2030)**

Further to comments received on the limit set for methanol in mother tinctures, a large enquiry was launched in 2004 (Pharneuropa 16.2). The results of this enquiry have now been examined by the HOM working party and it appears that a small number of productions do not comply with the 0.05 per cent V/V limit for certain

plant materials. Since the Commission Regulation (EEC) no. 1014/90 states a maximum of 1.5 per cent m/V (equivalent to about 1.9 per cent V/V) methanol content for alcoholic spirit drinks for human consumption, increasing the limit for mother tinctures, in justified cases, is not a safety issue.

A limit for methanol of 0.10 per cent V/V for the mother tincture of *Urtica dioica* has therefore been adopted.

MONOGRAPHS**Almond oil, virgin (0261)**

A slightly different composition of the fatty acids and unsaponifiable content has been reported, the limits for palmitoleic acid and unsaponifiable content have therefore been enlarged.

Neither criterion is a tracer for a possible adulteration.

Azithromycin (1649)

Due to the limited amount of impurity B available, it was not possible to produce the CRS by powder filling. It is therefore produced by evaporation. Description of reference solution (d) has been amended to take this into account.

Barium sulphate (0010)

The monograph prescribes pure barium sulphate without additives. The tests for phosphates and arsenic have been deleted since they are no longer relevant for current production. The test for sedimentation has also been deleted since it is only relevant for barium sulphate ready for use, i.e. with additives.

Calcitonin (salmon) (0471)

The whole monograph has been revised:

- to include calcitonin (salmon) obtained by rDNA technology;
- to make a reference to the general chapter on amino acid analysis (the test is now considered as an identity test);
- to delete the TLC identification test which is considered obsolete;
- to add a section on impurities.

Cetostearyl alcohol (0702)

The assay method has been revised in order to replace the packed column by a capillary column.

Modifications have been made to the test for appearance of solution, and to the test for iodine value.

Cetyl alcohol (0540)

The monograph has been totally revised to update and harmonise it with the revised monographs on cetostearyl alcohol and stearyl alcohol.

Chlorpromazine hydrochloride (0475)

The revision includes the replacement of the TLC in the test for related substances by an LC which allows an improved control of the impurities. Identification C has been withdrawn from the first series as it was considered unnecessary. The use of 0.1 M hydrochloric acid in the assay increases the reproducibility of the method.

Colistin sulphate (0320)

This monograph has been revised to specify how the calculation of content has to be performed under Assay. In addition, as polymyxin E is synonymous with colistin, colistin E1 is not correct and should read polymyxin E1 instead, names of the other components have also been changed accordingly.

Enoxaparin sodium (1097)

The monograph has been revised to allow for better quality control of the product that is currently marketed, while taking account of the knowledge of the structure of enoxaparin.

Erythropoietin concentrated solution (1316)

The monograph has been revised following adoption of batch 2 of *erythropoietin BRP* in which isoform 1 is present in such a small amount that it is not readily visible in the electropherogram. Moreover, the limits for isoforms 3 and 7 have been modified in the light of batch data for approved products.

Fluoxetine hydrochloride (1104)

In the test for related substances a solution containing 4-*trifluoromethylphenol R* is now injected as an alternative when this substance cannot be obtained by the *in situ* degradation of fluoxetine hydrochloride.

Goldenrod, European (1893)

The lower limit for flavonoids content has been tightened and an upper limit has been introduced to distinguish Goldenrod from European Goldenrod.

Due to the absence of leiocarposide in some European Goldenrod batches, a TLC identification has been replaced by that described in the Test section.

Both TLC and HPTLC plates have been tested and were not equivalent: consequently only TLC plates are described in this monograph.

Human albumin solution (0255)**Human normal immunoglobulin (0338)**

A second column is now cited in the test for distribution of molecular size, corresponding to currently used equipment.

Human coagulation factor VIII (0275)

The assay of von Willebrand factor now refers to the new general method and has been transferred from the Production section to the Assay section. Pending the availability of an International Standard calibrated for use in the collagen-binding assay, only the ristocetin cofactor assay may be used.

Human normal immunoglobulin for intravenous administration (0918)

This monograph has been revised to add a limit for anti-D antibodies, which have been associated with adverse

reactions in patients (S J Thorpe et al., *Vox Sanguinis*, 2003, 85, 80-84). A general method for determination of anti-D antibodies (2.6.26) is also published in Supplement 5.3. A biological reference preparation will be established for definition of the limit. Awaiting availability of this preparation, a suitable preparation is available from the National Institute for Biological Standards and Control, UK (code 02/228) and also a suitable negative control (code 02/226). The limit to be set is equal to the titre of reference preparation 02/228.

Furthermore, a second column is now cited in the test for distribution of molecular size, corresponding to currently used equipment.

Human plasma for fractionation (0853)

The monograph has been revised:

- to remove the requirement for testing for hepatitis C virus antibodies on the plasma pool;
- to transfer the Storage section under Production to have a mandatory requirement regarding storage and transport of frozen plasma; there is no substantial change to the existing requirements.

Hyoscyamine sulphate (0501)

The monograph has been revised to obtain 2 peaks of similar height in reference solution (c) used for the calculation of the resolution in the test for related substances.

Iceland moss (1439)

The test for other lichens species has been deleted. Usnic acid is not detected in all the batches tested and the test is therefore not significant.

Isradipine (2110)

In view of batch data from a manufacturer it is necessary to increase the limit for impurity A from 0.1 per cent to 0.2 per cent. Impurity A was subsequently transferred from the "other detectable impurities" section to the "specified impurities" section.

Macrogolglycerol ricinoleate (1082)

In the test for appearance of solution some products showed results closer to the limit BY_5 than to BY_6 ; since this material is yellow, BY_6 appears to be too stringent and a relaxation of the limit has therefore been made.

Magnesium carbonate, heavy (0043)**Magnesium carbonate, light (0042)**

Identification A, which allows differentiation between light and heavy magnesium carbonate has been revised to improve the wording of the test to give more precision.

Mannitol (0559)

The revision includes the following modifications:

- identification A: a detailed operating procedure is prescribed for the recrystallisation of the samples. This should allow for identical crystalline forms to be obtained, for the substance to be examined and the reference substance;
- conductivity: heating is necessary to allow the dissolution of the sample;

- related substances: a limit 'for any other impurity' has been introduced and the disregard limit has been decreased;
- water: a mixture containing formamide has been introduced as solvent to improve the dissolution of the sample.

Medroxyprogesterone acetate (0673)

Since the LC method in the test for related substances could not separate all impurities sufficiently, a new method has been adopted. In addition, a system suitability CRS is introduced to allow identification of the impurities where the limit is above 0.1 per cent or where a correction factor applies. Based on the review of recent production batches the limits for impurities have been tightened.

The specifications for specific optical rotation have been adapted due to the replacement of dioxan by acetone.

In the test for impurity F hexane has been replaced by heptane which is less toxic.

Naphazoline nitrate (0147)

In identification B, the absorbance ratio 287/280 nm has been deleted since measurement of the absorbance at 287 nm is difficult to perform on some instruments.

Neroli oil (1175)

This monograph has been revised to improve the control of adulteration, as neroli oil is amongst the most expensive essential oils on the market. After publication in *Pharmeuropa* 15.1, a chiral chromatography appropriate for this purpose has been introduced. Limits have been adapted to current ISO-norms.

Nortriptyline hydrochloride (0941)

In accordance with the new policy on this matter, a CRS has been established for comparison for the identification by IR, in replacement of the reference spectra.

Omega-3-acid ethyl esters 90 (1250)

In the test for oligomers it has been reported that when omega-3-acid ethyl esters 90 contain monoglycerides as residues from the manufacturing process, these monoglycerides may co-elute with the oligomers in the chromatogram obtained. This situation leads to an erroneously high content of oligomers and batch rejection. If the sample is saponified and undergoes a methylation step, the residual monoglycerides are converted into methyl esters, elute later, and no longer interfere with the oligomers determination. This additional methylation step has therefore been introduced as an alternative in cases where the result is too high due to the presence of residual monoglycerides.

Orciprenaline sulphate (1033)

The medium in the titration has been changed to improve the dissolution of the sample based on an experimental study of the EDQM laboratory.

Penicillamine (0566)

The name of the micro-organism used in the test for penicillin has been modified in compliance with the following publication: J. S. Tang and P. M. Grillevet, Reclassification of ATCC 9341 from *Micrococcus luteus* to

Kocuria rhizophila, *International Journal of Systematic and Evolutionary Microbiology*, 2003:53; 995-997.

Pentamidine diisetonate (1137)

A production section has been added as for the monograph on hexamidine diisetonate.

Phenoxyethylpenicillin potassium (0149)

The upper limit for content has been increased to 102.0 per cent as the assay is performed by LC.

Polymyxin B sulphate (0203)

This monograph has been revised to specify how the calculation for content has to be performed under Assay.

Ranitidine hydrochloride (0946)

The preparation of reference solution (c) in the test for related substances has been changed to facilitate the dissolution of the sample of CRS and to have a more suitable concentration to check the resolution.

Risperidone (1559)

Impurity G has been deleted in the other detectable impurities list because it is not separated from risperidone using the LC prescribed in the test for related substances.

Saccharin (0947)

Saccharin sodium (0787)

This monograph has been revised within the framework of international harmonisation.

Salbutamol (0529)

Salbutamol sulphate (0687)

It is not possible to obtain a high quantity of impurity I to establish a replacement CRS batch. Following a study of the Ph. Eur. laboratory showing that impurity I has a response factor similar to that of salbutamol, the impurity is quantified by comparison with salbutamol. Impurity I is only injected for identification purposes. This allows a reduction of the quantity of CRS provided to the users. The monograph will stay on the work programme for revision of the test for related substances.

Somatropin (0951)

Somatropin bulk solution (0950)

Somatropin for injection (0952)

As a result of a collaborative study involving manufacturers of somatropin and OMCLs, the isoelectric method for the determination of isoform distribution has been replaced by a capillary zone electrophoresis method.

Stearyl alcohol (0753)

The assay method has been revised in order to replace the packed column by a capillary column.

Streptokinase bulk solution (0356)

The specific activity included in the original Ph. Eur. monograph (600 IU/ µg of nitrogen) was based on a spectrophotometric determination. This method had a systematic error which became apparent recently when the analytical method to be used was specified as the Kjeldahl determination of nitrogen. In order to retain the original requirement for specific activity while changing to the Kjeldahl method, a value of 510 IU/ µg of nitrogen must be presented.

Sulfamethoxazole (0108)

In the test for related substances the pH of the mobile phase has been adjusted in the mixture (apparent pH). The Ph. Eur. laboratory has checked that equivalent results are obtained when the pH of the aqueous phase is previously adjusted to 5.3. Description of the mobile phase has been amended accordingly.

Ticarcillin sodium (0956)

The monograph describes the disodium salt. Moreover ticarcillin monosodium which is more stable than the disodium salt is now used as assay standard. The monograph was corrected in Supplement 5.1 to introduce this change. However as the disodium salt (*ticarcillin sodium CRS*) is no longer available as CRS, the IR is performed on ticarcillin acid obtained using a similar approach as in the monograph on cefazolin sodium. As IR no longer discriminates between the disodium and monosodium salt, reference to specific optical rotation has been necessary as additional identification.

In addition, the upper limit for content has been increased to 102.0 per cent in accordance with the standard policy for LC assays.

Tobramycin (0645)

This monograph has been revised to further detail the description of the LC method especially as regards to the quality of the reagents to be used. In addition, solutions are now prepared using the mobile phase instead of *water R*.

all-*rac*- α -Tocopherol (0692)

all-*rac*- α -Tocopheryl acetate (0439)

Following requirements of the general chapter on chromatographic separation techniques (2.2.46), the upper limit for content has been increased to 102.0 per cent.

Vitamin A (0217)

Following the recommendations of the Ph. Eur. laboratory after the establishment of batches 4 and 5 of *retinol acetate CRS*, the limits for the absorbance ratios in the test for related substances are now expressed to 2 decimal places (instead of 3).

Vitamin A concentrate (oily form), synthetic (0219)

Vitamin A concentrate (powder form), synthetic (0218)

Vitamin A concentrate (solubilisate/emulsion), synthetic (0220)

The monograph has been revised because in some cases it was observed that the saponification of retinol palmitate was not complete. To prevent this, preparation of the solutions has been improved as follows: introduction of a heating step; the amount of sample weighed is now fixed and BHT is introduced via the solvent (2-propanol).

In addition, based on the recommendations of the Ph. Eur. laboratory after establishment of batches 4 and 5 of *retinyl acetate CRS*, the limits for the absorbance ratios are now expressed to 2 decimal places (instead of 3).

Xylitol (1381)

The GC is used in the test for related substances and the assay. Additional test and reference solutions have been added in the assay to avoid saturation of the peak and to have a more suitable concentration of internal standard.

The monograph remains on the work programme. Experimental work is planned to try to replace the GC by an LC and if not possible, to use a capillary column in the GC.