

COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 4.5

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the June 2002 session. This information completes the modifications indicated by lines in the margin in the supplement. Hence, the information below is not necessarily exhaustive.

METHODS OF ANALYSIS

2.4.10. Lead in sugars

The text contained an error since it referred to a saturated solution of *ammonium pyrrolidinedithiocarbamate* at about 10 g/l. However, the solubility quoted by reagent suppliers is about 100 g/l. The mistake arose because a 10 g/l solution was found not to be clear and this was assumed to be due to the solubility of the reagent. The text has been modified to indicate a «clear 10 g/l solution». According to certificates of analysis from suppliers the reagent does give a clear solution.

2.4.14. Sulphated ash

This text has been revised to mention a silica crucible, which is the most commonly used type.

2.4.18. Free formaldehyde

Method B for determination of free formaldehyde in vaccines has been revised following work carried out in the Biologicals Quality Monitoring Working Group of VICH. The method is now presented as an assay (with a calibration curve) rather than as a limit test. *Polysorbate 80 R* is no longer included in the reaction mixture since it has been found unnecessary and its presence raises the baseline absorbance and can compromise the accuracy of the test. The method as presented has been tested in an international collaborative trial (P F Ross et al., Biologicals, 2002, 30, 37-41).

MATERIALS/CONTAINERS

3.1.4. Polyethylene without additives for containers for preparations for parenteral use and for ophthalmic preparations

3.1.5. Polyethylene with additives for containers for preparations for parenteral use and for ophthalmic preparations

The wording of the IR identification has been clarified as not all types of polyethylene show maxima at all the wave-numbers cited. The presence of a certain number

of the maxima and comparison with the type sample establishes the identity of the material.

3.1.3. Polyolefines

The wording of the IR identification has been clarified as not all polyolefines show maxima at all the wave-numbers cited. The presence of a certain number of the maxima and comparison with the type sample establishes the identity of the material.

MONOGRAPHS

Amisulpride (1490)

In the test for impurity A, the concentration of reference solution (b) has been increased 10-fold to allow better detection of amisulpride to check the system suitability.

Bacitracin (0465)

Bacitracin zinc (0466)

The TLC method under identification has been replaced by a simpler TLC method in order to avoid preliminary hydrolysis.

Beeswax, white (0069)

Beeswax, yellow (0070)

The monograph has been revised in order to delete the ratio of ester value to acid value which was considered meaningless with regard to the detection of adulteration by other waxes.

Benzylpenicillin potassium (0113)

Benzylpenicillin sodium (0114)

In the assay, the description of the preparation of the solutions has been amended, following degradation

problems. The repeatability requirement has been deleted as chapter 2.2.46 applies.

Buflomedil hydrochloride (1398)

This monograph has been revised to tighten the specifications of the tests for appearance of solution and for pH and thus improve the purity level required.

Carisoprodol (1689)

The use of non-silanised silica gel plates allows a better separation in the test for related substances.

Chloroquine phosphate (0544)

The test for water by semi-micro determination has been replaced by a test for loss on drying (also in the USP) as difficulties were encountered when performing the test for water: $n = 6$, $RSD = 20\%$, the substance was not completely dissolved. The limits of the test remain unchanged.

Dextropropoxyphene hydrochloride (0713)

The test for pH has been replaced by a test for acidity/alkalinity as the pH of the substance is 2.3 and,

according to the technical guide, an acidity/alkalinity test is therefore more appropriate.

Dimeticone (0138)
Simeticone (1470)

The IR identification has been modified since the concept of a type sample is applied to plastic materials for containers and not to active substances or excipients.

Dosulepin hydrochloride (1314)

The test for impurity E (Z-isomer) and related substances has been modified to improve the separation of the isomers and of the impurities.

Econazole nitrate (0665)

Since identification by IR is sufficient, the other identification tests have been deleted. The limits of content have been tightened in the light of the purity of the samples. The test for appearance of solution has been deleted as the substance is not for parenteral use.

Fibrin sealant kit (0903)

Coagulation factor XIII is now specified as an optional constituent of Component 1. Consequently, the Definition section has been modified.

Flupentixol dihydrochloride (1693)

The monograph has been revised to indicate that under certain circumstances a doubling of peaks and spots may be observed in the LC test for impurity F and in the TLC analyses.

Due to the solubility of the substance, the preparation of solutions for the assay for Z-isomer has been modified.

Gelatin (0330)

The monograph on gelatin has been revised to bring it into line with current quality standards for the product, notably in the food sector, which are more demanding than the monograph at present in force. A detailed briefing was presented with the monograph published in Pharmeuropa 13.3.

Definition. The use of enzymatic hydrolysis is now mentioned; gelatin obtained from fish and poultry are now specifically mentioned. Non-gelling grades are also mentioned.

Characters. The statement on isoelectric point has been modified to give more information. A statement on colour and clarity of solution has been added since the test has been deleted (see below).

Identification. A distinction is made between gelling and non-gelling grades. The identification is rather weak for non-gelling grades and it is proposed to add, for a future revision, a test for hydroxyproline, an amino acid typical of gelatin.

Appearance of solution. The test has been deleted. It was not applicable to many grades of gelatin in current use and was rather to be seen as a specification agreed between supplier and user for a particular purpose.

Phenolic preservatives. The test has been deleted because it only covered a small number of antimicrobial preservatives (parahydroxybenzoates and pentachlorophenol).

Sulphur dioxide. The limit has been reduced to 50 ppm, in line with food sector requirements.

Peroxides. The limit has been reduced to 10 ppm, in line with food sector requirements. This limit requires the use of commercially available test strips.

Gel strength. The test apparatus has been adapted to correspond to that currently used by the gelatin industry. The test is now required for all gelling grades since it is one of the most important quality parameters.

Iron, Chromium, Zinc and Heavy metals. Specific tests have been included for these potential contaminants and the general test for heavy metals has been deleted since it did not provide adequate control. Tests for other metals (Hg, Pb, Cd, As) have not been included even though the food sector has limits. These metals are highly unlikely contaminants and testing requires methods not usually available in pharmaceutical industry control laboratories.

Gentamicin sulphate (0331)

In the test for methanol, the GC method has been replaced by reference to the general method applied for the control of residual solvents.

The limit for bacterial endotoxins has been tightened, as in the USP monograph because of changes in the administration schedule (single daily dose).

Glibenclamide (0718)

The test for appearance of solution has been deleted as glibenclamide is not used parenterally.

Glucagon, human (1635)

Specific limits for the symmetry factor are given in the test for related proteins and the assay as in most cases the symmetry was found to be less than 1, and in several cases below the limit of 0.8 given in general chapter 2.2.46.

Glycerol (0496)

Glycerol (85 per cent) (0497)

The GC test for impurity A and related substances has been modified and quantification of the impurities is by comparison with the peak due to impurity A instead of the peak due to glycerol since poor reproducibility was observed with the peak due to glycerol.

Guaifenesin (0615)

The method for the assay has been revised to avoid use of arsenite solution.

Heparins, low-molecular-mass (0828)

Identification C which describes assessment of the mass-average molecular mass of low-molecular-mass heparins using size-exclusion chromatography was not sufficiently detailed to enable evaluation of the substance to be examined as prescribed in specific

monographs. Therefore specific instructions for the use of a calibration curve have been introduced.

Ketotifen hydrogen fumarate (1592)

The reference solutions in the test for related substances has been modified such that the resolution could be verified on 2 peaks of similar height.

Macrogols (1444)

The test for formaldehyde with a limit of 15 ppm was introduced in the monograph because of the risk of cross-linking of gelatin in the presence of formaldehyde and its impact on dissolution and disintegration properties of soft capsules. However, it has since become apparent that a limit of 15 ppm would lead to a very short shelf life for the macrogols and the limit has therefore been raised to 30 ppm.

Naphazoline nitrate (0147)

The identification for nitrates has been replaced by a new test without pre-treatment, which does not use nitrobenzene as a reagent.

Parnaparin sodium (1252)

The identification test describes assessment of molecular mass of parnaparin sodium using size-exclusion

chromatography. It has been noted that the description of the method is not sufficiently detailed to enable a good evaluation of samples of parnaparin sodium in the lower molecular mass ranges. A statement requesting a system suitability verification using an in-house standard has therefore been introduced.

Pefloxacin mesilate dihydrate (1460)

A production section related to alkyl mesilates has been introduced.

Polymyxin B sulphate (0203)

The microbiological assay has been replaced by an LC method. The quantitative analysis is based on the content of the major component, polymyxin B1.

Roxithromycin (1146)

The test for related substances has been revised to obtain better separation and less peak tailing: the use of an end-capped column is now prescribed. The test for ethanol and toluene has been deleted according to the information given in General Chapter 5.4 on residual solvents.

VACCINES FOR HUMAN USE

Varicella vaccine (live) (0648)

The monograph indicated a minimum virus titre of 2.0×10^3 PFU, which until recently corresponded to all available vaccines. The monograph has been revised

because a new vaccine has been licensed in Italy, based on a modified OKA strain, with a minimum titre of 1350 PFU. A Mutual Recognition Procedure for the product has begun.

GUIDE TO SAFETY AND QUALITY ASSURANCE FOR ORGANS, TISSUES AND CELLS

1st Edition

The non-commercialisation of substances of human origin is one of the basic principles supported by the Council of Europe. This principle was enshrined in Resolution (78) 29 and confirmed by the European Ministers of Health at their Ministerial Conference held in Paris in 1987.

The safety and dignity of the donor and the recipient are the ethical concerns followed by the European Health Committee. To this end a Group of Experts was entrusted to prepare this guide, which includes standards for procurement, preservation, processing and distribution.

The legal provisions which should be complied with in the area of the transplantation of organs, tissues and cells are enacted in the additional protocol to the Convention on Human Rights and Biomedicine. The protocol is appended in its entirety to this guide.

The Guide to safety and quality assurance will be of interest to health professionals working in transplantation centres, organ, tissues and cell exchange organisations, legislators and all those working in the field of transplantation. This guide will be regularly updated, in line with the latest technical progress

Price: **13.00 EUR**

The 1st Edition of the Guide can be obtained in English and French from:

Council of Europe Publishing - Sales Unit
Ms Sophie Lobey, F-67075 Strasbourg Cedex, France
Tel: +33 (0) 3 88 41 22 63 - Fax : +33 (0) 3 88 41 27 80

Questions and comments on the content should be sent directly to the division in charge:

Council of Europe,
Health Division,
Mr Karl-Friedrich Bopp,
F-67075 Strasbourg Cedex, France
Tel: +33 (0) 3 88 41 22 14 - Fax: +33 (0) 3 88 41 27 26
E-mail: karl-friedrich.bopp@coe.int