

REVISED TEXTS PUBLISHED IN SUPPLEMENT 4.2

Here follows a summary of the technical modifications to the revised texts adopted by the European Pharmacopoeia Commission at the June 2001 session. This information completes the modifications indicated by lines in the margin in the supplement. Hence, the summaries below are not necessarily exhaustive.

GENERAL CHAPTERS

2.6.13. Microbiological examination of non-sterile products (test for specified micro-organisms)

Further to the revision of the 3 monographs on water, the description of agar medium S had to be added to chapter 2.6.13.

3.1.11. Materials based on non-plasticised poly(vinyl chloride) for containers for dry dosage forms for oral administration

One of the permitted additives in non-plasticised PVC interferes with the test for absorbance of solution S2. The test has been adapted to cope with materials containing this additive.

MONOGRAPHS

Acebutolol hydrochloride

The TLC prescribed for the test for related substances has been replaced by a HPLC method that assures a good separation of the 11 identified impurities, from both acebutolol and from each other. Method D for heavy metals has been replaced by method E following the results from the EP laboratory.

Ammonium bromide

This monograph was revised and harmonised with the monographs on potassium bromide and sodium bromide. A test for magnesium and alkaline-earth metals was added which made the test for calcium no longer necessary.

Angelica root

After analysis by TLC of Lovage root and Angelica root, the method was improved by using eugenol and coumarin as reference substances. Umbelliferone, which does not migrate on the plate, was deleted. It is also proposed to examine the plate at 254 nm to mark the zones of both reference substances on the chromatogram of the reference solution and then examine at 365 nm. Spraying with an alcoholic solution of potassium hydroxide increases the intensity of zones, including a blue zone in the lower third of the chromatogram for Lovage. This zone, which only appears after spraying, is a source of considerable confusion since the absence of falsification of Lovage by Angelica is confirmed only by the absence of a blue fluorescent zone in the lower third. For harmonisation of both monographs, the spraying with an alcoholic solution of potassium hydroxide was deleted.

Butyl parahydroxybenzoate

Following experimental work to check the precision of the assay, the content limits have been widened and the operating conditions have been slightly changed.

Carbomers

The limit for the test for the loss on drying was increased to 3.0 per cent because of a new carbomer product, carbomer 71G®, a granular form of carbomer 971P® on the market. The new product is similar to the existing form except for the particle size. The production of carbomer 71G® involves taking the original powder 971P® and compacting it. This exposes carbomer 71G® to atmospheric moisture, hence the necessity to increase the limit for the loss on drying.

Cefadroxil monohydrate

Due to the large polarity difference between impurities a gradient for the HPLC was unavoidable. Furthermore, the upper limit of content has been increased to 102.0 per cent as the assay is carried out by HPLC. The mobile phase in identification B has been changed according to the general revision and harmonisation of the identification of cephalosporins.

Cefazolin sodium

As this substance is only for parenteral use, IR has replaced the current identification tests A and B.

Following an inquiry of manufacturers the limit for total impurities in the related substances test has been reduced from 5 to 3.5 per cent.

Cefoxitin sodium

The substance being used parenterally, the second identification series has been deleted.

Ceftazidime

The monograph has been revised following the request received after establishment of the CRS. The LC method for pyridine (= impurity F) was modified to improve the separation between the principal peak and the peak due to pyridine. A system suitability test has been introduced.

Cholesterol

This monograph has been revised to describe a more usual column in the assay by GC. The chromatographic conditions have been slightly adapted accordingly resulting in an improved separation (higher resolution).

Clindamycin hydrochloride

The GC method in the test for related substances and the Assay has been replaced by a HPLC method. The proposed method, already used by the main producers and published in the USP 23, gives a good separation between clindamycin and its related substances.

The initial system suitability was a resolution of at least 3.0 between 7-epiclindamycin (Rt about 8 min) and clindamycin (Rt about 10 min) or a resolution of at least 2.4 between clindamycin B (Rt about 6.5 min) and 7-epiclindamycin.

Unfortunately none of these impurities are available as reference standards due to extremely high costs and time of synthesis. Therefore relative retentions are given under system suitability and a chromatogram is given with the CRS.

Cyanocobalamin

During the establishment of the CRS, it was checked that methylene chloride could be used instead of chloroform in the TLC under Identification B.

Dexamethasone

The preparation of the test solution in the test for related substances was modified to improve the resolution.

Erythromycin stearate

This monograph has been revised to express the contents only as the base and no longer as stearate salts (conversion factor no longer needs to be applied in the assay), to introduce the relative retentions of all the related substances and correction factors for impurities E and F to take into account their high response and a limit for the total impurities. Identification B is now part of Identification A because IR alone does not distinguish between the base and the stearate.

Glyceryl trinitrate solution

The results obtained for the assay with the currently published monograph were too low. An alternative method was adopted and the limits revised accordingly. The description of the reagent sodium nitrite is also revised to add a method for the assay.

Human albumin solution

In the test for pyrogens, doses administered to rabbits for albumin solution containing 150 g/l to 250 g/l of protein are not in line with the maximal human doses per kilogram of human body weight injected to patients. Thus patients are often given more than the rabbit and there are no safety margins. The dose to be examined was increased to 5 ml for albumin solution containing 150 g/l to 250 g/l of protein.

Human anti-D immunoglobulin for intravenous administration

Some preparations, obtained by use of a chromatographic process, were unable to comply with the specification in the test for prekallikrein activator (PKA). From data published in the literature and in the light of the small volume injected into patients, it was concluded that there is no clinical relevance to test for PKA. Therefore the PKA test has been deleted.

Human coagulation factor VIII

In the test for pyrogens, doses administered to rabbits are not in line with the maximal human doses per kilogram of human body weight injected to patients. Thus patients are often given more than the rabbit and there are no safety margins. The dose to be examined was increased to a volume equivalent to 50 IU of factor VIII activity.

Human coagulation factor IX

In the test for pyrogens, doses administered to rabbits are not in line with the maximal human doses per kilogram of human body weight injected to patients. Thus patients are often given more than the rabbit and there are no safety margins. The dose to be examined was increased to a volume equivalent to 50 IU of factor IX activity.

Ibuprofen

This monograph was revised in order to control the additional impurities: introduction of a gradient system in the HPLC method (related substances test) in order to limit additional impurities, and introduction of a new test (GC method) covering 3-(4-isobutylphenyl)propionic acid (impurity F).

Isomalt

Isomalt CRS may contain a certain amount of mannitol and sorbitol and to allow correct quantification of the related substances, the preparation of the solutions used in the LC method has been modified.

Ivermectin

The structure of impurity E (currently the 2-epimer of H_2B_{1a}) was not correct, this impurity being in fact the 12-demethyl-12-ethyl derivative of H_2B_{1a} . Impurity F has also been changed in the same way since it corresponds to the derivative obtained from the minor compound of ivermectin (H_2B_{1a}).

Lovage root

The replacement of chlorinated solvents was investigated: it seems that a clear differentiation of Lovage root and Angelica root may be obtained only by using a mobile phase composed of methylene chloride.

After analysis by TLC of Lovage root and Angelica root, it is proposed to withdraw methylene chloride from the test solution and to improve the method by adding coumarin as second reference substance. The TLC tests in the two monographs have now been harmonised.

Mebendazole

The content limits were tightened to 99.0-101.0 per cent, based on the results obtained for the samples examined.

The appearance of the test solution was deleted since there is no parenteral use, nor coloured impurities.

Methyl parahydroxybenzoate

Following experimental work to check the precision of the assay, the content limits have been widened and the operating conditions have been slightly changed.

Mexiletine hydrochloride

The former Identification tests A, B and D have been deleted since mexiletine hydrochloride is presumably not used in pharmacies.

A TLC test for impurity D has been introduced, since it cannot be separated from mexiletine hydrochloride by the HPLC method because the structures of these 2 compounds are too similar.

Norethisterone acetate

A UV detection at 210 nm has been incorporated in the related substances test. Furthermore, UV detection at 254 nm has been maintained to cover at the same time the impurities absorbing at around 240 nm and those absorbing at 280 nm. For both detection wavelengths,

limits for individual and total impurities have been introduced. A number of outdated identity tests were deleted.

Pethidine hydrochloride

The assay has been revised to avoid use of mercuric acetate: the EP laboratory has checked that an alkalimetric titration can replace the current non-aqueous titration.

Potassium bromide

For the identification of bromides, reaction (a) is sufficient.

The 3 monographs on ammonium bromide, potassium bromide and sodium bromide are harmonised.

Potassium clavulanate

The LC method used in the related substances test was found to be unsatisfactory due to the high pressure in the column. The revised method is identical to that described in the USP monograph.

The specific test for 1,1-dimethylethylamine has been replaced by a test able to detect different aliphatic amines.

The test for potassium clavam-2-carboxylate was deleted as although it appeared to be a potential impurity it was never found in commercial batches taken from various sources.

Povidone

Test for impurity A: the mobile phase was modified to permit the separation of oligomers and other impurities from the monomers of low molecular weight povidone, and a time limit for stopping the elution of the pre-column is stated.

Povidone, iodinated

Production: since the introduction of chapter 5.4 on residual solvents, the two main producers of povidone-iodine do not satisfy the limit of 0.5 per cent of formic acid (class 3 solvent). To obtain a stable povidone-iodine the povidone used has to contain 1-2 per cent of formic acid. The formic acid is added to the povidone before its spray-drying and before the control according to the monograph. It is needed to react with the added iodine forming iodide which is a part of the complex between povidone, iodine and iodide (= povidone-iodine). The final povidone-iodine does not contain any formic acid because it reacts completely with the added iodine.

The Production section was revised to increase the formic acid limit to 2 per cent for the Povidone used.

Propyl parahydroxybenzoate

Following experimental work to check the precision of the assay, the content limits have been widened and the operating conditions have been slightly changed.

Riboflavine

A new crystalline form is now available. This new form shows superior pharmaceutical technical characteristics especially with respect to solubility and flowability. The monograph has therefore been revised in order to cover both crystalline forms.

Sodium bromide

For the identification of bromides, reaction (a) is sufficient.

Thus the 3 monographs on ammonium bromide, potassium bromide and sodium bromide are harmonised.

Sodium sulphate, anhydrous

Addition under Identification of a cross-reference to the test for loss on drying to differentiate sodium sulphate anhydrous from the decahydrate form.

The tests for iron, calcium and magnesium are only necessary when the substance is for parenteral use; the test for arsenic is deleted.

The limit for the loss on drying was lowered from 5.0 per cent to 0.5 per cent (*the line in the margin of the text published in the supplement is missing*).

The Assay method was replaced by a titration with an ion-selective electrode, which is more precise and easier to perform.

Sodium sulphate decahydrate

Addition under Identification of a cross-reference to the test for loss on drying to differentiate sodium sulphate decahydrate from the anhydrous form.

The tests for iron, calcium and magnesium are only necessary when the substance is for parenteral use; the test for arsenic is deleted.

The Assay method was replaced by a titration with an ion-selective electrode, which is more precise and easier to perform.

Sorbitol

Various crystalline forms are possible for sorbitol. The recrystallisation described in identification A does not give a single crystalline form and it has not been possible to find a suitable recrystallisation method. Thus the identification by infrared absorption spectrophotometry has been deleted.

Thiamine hydrochloride

The acid base titration currently in force has been replaced by a non-aqueous titration similar to the one described for thiamine nitrate.

Trolamine

The packed column used in the test for related substances has been replaced by a capillary column.

The limit for diethanolamine was decreased to 0.5 per cent and that for ethanolamine to 0.1 per cent. This is to minimise the risk of formation of the carcinogenic impurity *N*-nitrosodiethanolamine that develops mainly from diethanolamine during storage of trolamine.

Water for injections

Water, highly purified

Water, purified

The conditions for the determination of the total viable count should be changed (R2A medium).

Xylitol

The preparation of discs for the identification by infrared absorption spectrophotometry results in a spectrum of little use (disproportionate or attenuated absorption bands). It has been prescribed to carry out the IR spectrum using a dispersion of the substance in liquid paraffin.

VACCINES FOR HUMAN USE

Diphtheria and tetanus vaccine (adsorbed)

The test for specific toxicity is included as a validation requirement under Production rather than under Tests.

The details of production have been deleted and referred to the monographs Diphtheria vaccine (adsorbed) and Tetanus vaccine (adsorbed).

The details of the identification tests are cited as examples.

Diphtheria and tetanus vaccine (adsorbed) for adults and adolescents

The test for specific toxicity is included as a validation requirement under Production rather than under Tests.

The details of production have been deleted and referred to the monographs Diphtheria vaccine (adsorbed) and Tetanus vaccine (adsorbed).

The details of the identification tests are cited as examples.

Diphtheria, tetanus and pertussis vaccine (adsorbed)

The test for specific toxicity of diphtheria and tetanus components is included as a validation requirement under Production rather than under Tests.

The details of production have been deleted and referred to the monographs Diphtheria vaccine (adsorbed), Tetanus vaccine (adsorbed) and Pertussis vaccine (adsorbed).

The minimum number of mice used in the test of the pertussis component has been reduced to 5; allowance for repetition has been added.

The details of the identification tests are cited as examples.

Diphtheria vaccine (adsorbed)

The test for specific toxicity is included as a validation requirement under Production rather than under Tests.

The tests for residual toxicity and irreversibility of toxoid have been combined, a new text has been introduced.

The details of the identification test are cited as examples.

Diphtheria vaccine (adsorbed) for adults and adolescents

The test for specific toxicity is included as a validation requirement under Production rather than under Tests.

The details of production have been deleted and referred to the monograph Diphtheria vaccine (adsorbed).

The details of the identification test are cited as examples.

Pertussis vaccine

The details of production have been deleted and referred to the monograph Pertussis vaccine (adsorbed).

The minimum number of mice used in the test of the pertussis component has been reduced to 5; allowance for repetition has been added.

Pertussis vaccine (adsorbed)

The minimum number of mice used in the test for specific toxicity of the pertussis component has been reduced to 5; allowance for repetition has been added.

Tetanus vaccine (adsorbed)

The test for specific toxicity is included as a validation requirement under Production rather than under Tests.

The tests for residual toxin and irreversibility of toxoid have been combined.

The details of the identification test are cited as examples.

Typhoid polysaccharide vaccine

A change has been made to the limit for bacterial endotoxins. In the existing monograph a defined limit is given but in view of the fact that recently licensed products have a different level of bacterial endotoxins, in order to align the monograph with licenses, a product-specific limit is now proposed. The amount of bacterial endotoxins present is more of a measure of consistency of production than a safety indicator.