

COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 4.3

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

METHODS OF ANALYSIS

2.2.6. Refractive index

The reference liquids for calibration referred to in this general chapter do not correspond to the Ph. Eur. definition of reference substances. Certified reference materials should be used. The reference substances in question will be removed from the Ph. Eur. catalogue.

2.5.4. Iodine value

Addition of a new method based on the ISO standard.

2.7.12. Assay of heparin in coagulation factors

The former assay method was based on the inhibition of coagulation factor IIa, it had a very limited working range for linear results and was poorly adapted to some preparations. The method was revised and is based on measurement of the inhibition of coagulation factor Xa, which does not have these shortcomings.

2.9.19. Particulate contamination: sub-visible particles

Spherical particles CRS referred to in this general chapter do not correspond to the Ph. Eur. definition of reference substances and their suitability cannot be verified by the group of experts or the Ph. Eur. laboratory. Certified reference materials or reference materials traceable thereto should be used. Spherical particles CRS will be removed from the catalogue of reference substances.

2.9.22. Softening time determination of lipophilic suppositories

Minor revision further to a request from the manufacturer of apparatus A. The same modification has been introduced for apparatus B to be consistent.

GENERAL TEXTS

5.1.2. Biological indicators of sterilisation

Dry-heat sterilisation: due to unavailability of spores of *Bacillus subtilis* with a D-value at 160 °C of 5 min to 10 min, the D-value was amended to 1 min to 3 min. This harmonises the Ph. Eur. requirement with the USP.

Gas sterilisation: the three decontaminants mentioned (hydrogen peroxide, peracetic acid and formaldehyde)

were not used in connection with medicines but rather for the "sterilisation" of medical surgical surfaces and devices (which are no longer part of the Pharmacopoeia). In most cases, ethylene oxide is used for the gas sterilisation of starting materials and finished products. Other gases are used only when there is no suitable alternative.

GENERAL MONOGRAPHS

Extracts (0765)

In the revised monograph on extracts (0765), the monograph on tinctures (0792) has been incorporated as a sub-section. Hence, the existing tincture monograph is therefore suppressed.

Immunosera for human use, animal (0084)

General revision to adapt the monograph to modern control methods for animal immunosera.

MONOGRAPHS

Aceclofenac (1281)

In the test for related substances, the description of the stationary phase has been specified to correspond to the one used during the development of the method.

Acitretin (1385)

The concentrations of the solutions in the assay have been decreased to avoid saturation of the detector and thus obtain a linear response.

Amiodarone hydrochloride (0803)

The identification section has been revised as one identification series is considered sufficient. In the tests section, the thin-layer chromatography is kept only to detect impurity H and other related substances are now determined by liquid chromatography.

Amphotericin B (1292)

The assay has been revised following the establishment of the CRS.

Apomorphine hydrochloride (0136)

The test for related substances has been modified as a resolution of 5 can be difficult to achieve depending on the column used. The resolution has been decreased to 2.5 after verification by the European Pharmacopoeia laboratory.

Calcium chloride dihydrate (0015)

The title was revised to specify the degree of hydration. An identification test has been added to distinguish between the existing different hydrated forms.

Cefalexin monohydrate (0708)

The title was revised to specify the degree of hydration. The upper limit of content has been increased to 102.0 per cent as the assay is carried out by HPLC.

Cefradine (0814)

Following a request for revision, the limit for absorbance under Appearance of solution has been increased and the storage temperature changed to 2-8 °C for stability reasons.

Cefuroxime sodium (0992)

In the test for related substances, the LC method has been modified following a request for revision and after verification by the European Pharmacopoeia laboratory.

Cellulose acetate phthalate (0314)

Revision of the text following the international harmonisation process.

Cetrimide (0378)

As a consequence of the difficulty in obtaining methyl green, identification B has been replaced by a precipitation reaction that is easier to perform.

Chamomile flower, roman (0380)

Following a request for revision, the test for water has been replaced by the test for loss on drying. Comparable results have been obtained with the two methods since the content of essential oil in roman chamomile flower is very low. The limit of the test has been increased so that most of the values can comply with the test.

Chlorprothixene hydrochloride (0815)

Chlorprothixene hydrochloride CRS is spiked with about 2 per cent of *E*-isomer. As the IR spectrum of the CRS differs from the IR spectrum of the pure substance, pre-treatment of the substances before recording the IR spectra is prescribed.

Colistimethate sodium (0319)

The limit for loss on drying has been increased to 5.0 per cent as in other peptide antibiotics. Due to the hygroscopicity of the compound, the existing limit was too low and difficult to achieve.

Cyproheptadine hydrochloride (0817)

As the substance sublimes under the conditions specified in the test for loss on drying, the test has been replaced by a determination of water by Karl Fischer titration.

Cysteine hydrochloride monohydrate (0895)

In the test for ninhydrin-positive substances, the concentration of *N*-ethylmaleimide in the *N*-ethylmaleimide in alcohol solution has been doubled to improve the visualisation of impurities.

Devil's claw root (1095)

The species *Harpagophytum zeyheri*, which is more widely used, has been added to the definition in order to cover all products on the market. The two species cannot be distinguished by a botanical identification but only with a highly sophisticated HPLC method. The limit for total ash has been increased so that most of the values can comply with the test.

Dexamethasone (0388)

The melting point under Characters has been deleted following results from the European Pharmacopoeia laboratory.

Diethylene glycol monoethyl ether (1198)

The assay has been deleted since the substance is considered as an excipient and is fully controlled by the tests. The definition has been modified to take account of these changes. The method for the test for related substances has been revised to improve the separation and the limits have been modified. The resolution was improved in the test for ethylene oxide.

Docosate sodium (1418)

The monograph published in Supplement 4.1 to the 4th Edition is not correct. The monograph published in the 4th Edition should be used instead with the following change in the test for chlorides:

“...Not more than 0.5 ml of 0.1 M silver nitrate is required to change the colour of the indicator from yellow to orange.”

The monograph will be republished as described above in Supplement 4.3.

Droperidol (1010)

Following a request for revision, another quality of tetrabutylammonium hydrogen sulphate has been described to ensure no problem is encountered in the LC for related substances.

Enalapril maleate (1420)

The solubility has been corrected according to the results obtained from the European Pharmacopoeia laboratory.

Erythromycin ethylsuccinate (0274)

The TLC method in the test for related substances and the microbiological assay have been replaced by an HPLC method with prior hydrolysis. This method is the same as that used in the other erythromycin monographs.

Etoposide (0823)

The results obtained in the test for loss on drying vary substantially and are lower than those obtained in the determination of water by Karl Fischer titration. The test for loss on drying has been replaced and the specifications changed.

Ferrous gluconate (0493)

Based on batch data, the lower limit of the test for loss on drying has been decreased from 7.0 to 5.0 per cent (mean of obtained results: 6.4 per cent).

Ferrous sulphate heptahydrate (0083)

The title was revised to specify the degree of hydration. An identification test has been added to distinguish between the existing different hydrated forms.

Flunitrazepam (0717)

The limits for content have been tightened in the light of the purity of the samples examined.

Folic acid (0067)

Impurities A to F are identified and qualified impurities. However, there are other impurities in current licensed products in Europe. Those unidentified impurities, present at levels less than 0.5 per cent, are qualified. The revised monograph takes account of this situation.

Glycine (0614)

This monograph has been revised to add the test for ninhydrin-positive substances (as described in the other monographs on amino acids).

Haloperidol (0616)

Following a request for revision, another quality of tetrabutylammonium hydrogen sulphate has been described to ensure no problem is encountered in the LC for related substances.

Human normal immunoglobulin (0338)

To take into account a preparation on the European market that has a pH specification of 5.0 - 5.5, the lower pH limit has been changed from 6.4 to 5.0.

Isopropyl myristate (0725)**Isopropyl palmitate (0839)**

The relative density is no longer an identification and purity criterion and has been placed under Characters. The test for sulphated ash was replaced by a test for total ash.

Lactulose (1230)**Lactulose, liquid (0924)**

Since it has not been possible to obtain a sample of epilactose in sufficient quantity to prepare a new CRS batch, lactulose for system suitability CRS has been prepared from a spiked sample of lactulose. This CRS replaces epilactose CRS as well as the use of reagents for the 4 other impurities. It is used to check the system suitability and to identify the impurities.

Metixene hydrochloride (1347)

The spots due to thioxanthene and thioxanthone are not completely separated in the TLC for related substances but can be distinguished by their difference of colour. Therefore, the colours of the two spots have been included.

Metoprolol succinate (1448)**Metoprolol tartrate (1028)**

The monographs on metoprolol tartrate and metoprolol succinate have been revised to improve the test for related substances. The column indicated gives much better separation than the previous one. Therefore, impurity A is now used for the resolution test because with the new system impurity D gave a resolution factor which was too high. The transparency statements of both monographs have been harmonised. Impurities I, K and L of metoprolol tartrate have been deleted since they are not found in samples.

Noradrenaline hydrochloride (0732)**Noradrenaline tartrate (0285)**

As the reagent used in identification E (diethoxytetrahydrofuran) will no longer be available, the second identification series has been deleted.

Omega-3-acid ethyl esters 90 (1250)

The monograph has been revised to improve the system suitability test in the test for oligomers. The test for conjugated dienes was replaced by a test for absorbance after thorough checking had been carried out on production batches. Reference to general method 2.4.29 (Composition of fatty acids in oils rich

in omega-3-acids) has been included in the assay of EPA, DHA and Total omega-3-acids ethyl esters.

Omega-3-acid triglycerides (1352)

The test for conjugated dienes was replaced by a test for absorbance. Reference to general method 2.4.29 (Composition of fatty acids in oils rich in omega-3-acids) has been included in the assay of EPA, DHA and Total omega-3-acids ethyl esters.

Paraffin, light liquid (0240)

Paraffin, liquid (0239)

The IR identification employed the reference spectrum of hard paraffin. Since significant differences were observed between the IR spectra of hard paraffin and liquid and light liquid paraffin, a new reference spectrum for liquid paraffin was established and the monographs have been corrected accordingly.

Pilocarpine hydrochloride (0633)

Pilocarpine nitrate (0104)

As isopilocarpine nitrate CRS is no longer available, it has been replaced by a mixture for system suitability containing pilocarpine and isopilocarpine.

Piperacillin (1169)

Following a request for revision, the limits for specific optical rotation were checked by the European Pharmacopoeia laboratory and have been modified.

Pivampicillin (0852)

Reference is made to general method 2.4.26 in the test for *N,N*-dimethylaniline. However, the preparation of the test solution is different from that described in the general method.

Pivmecillinam hydrochloride (1359)

This was the only monograph where a method for the test for *N,N*-dimethylaniline was missing. The European Pharmacopoeia laboratory has checked that general method 2.4.26, Method A applies. The test is now located with the other tests.

Poloxamers (1464)

Under identification, an alternative was introduced in order to replace IR by NMR, since the latter has to be carried out under Tests. In the test for ethylene oxide, propylene oxide and dioxan, the head-space gas chromatography method was revised as the previous method was complicated, time consuming and there was co-elution of aldehydes (acetaldehyde) and ethylene oxide. A commercially available standard of ethylene oxide in methylene chloride can be used. The limit for dioxan has been increased to 10 ppm for the sake of harmonisation.

Praziquantel (0855)

As this substance is not handled in pharmacies, only IR identification has been kept. The melting point has been deleted since the substance shows polymorphism. The test for appearance of solution has been deleted as the substance is not for parenteral use. The limit for the test for heavy metals has been changed from 10 to 20 ppm according to the technical guide indications. The assay by UV spectrophotometry was not the best choice as the known impurities have a very high specific absorption at the assay wavelength i.e. 265 nm. The permitted maximum of impurities (0.5 per cent) would thus result in an assay value of 130 per cent. This method has therefore been replaced by a more specific and accurate HPLC method. The limits for content have been reviewed accordingly. At the wavelength chosen for the related substances test, 210 nm, differences in specific absorption are negligible.

Pyridoxine hydrochloride (0245)

Several manufacturers had reported that the current titration gave higher results than the previous non-aqueous titration. The Ph. Eur. laboratory has confirmed that with the current method the first inflexion point is barely detectable, thus leading to very variable results. With the titration conditions of thiamine hydrochloride, the results obtained are similar to those obtained with the former non-aqueous titration in the presence of mercuric acetate.

Saccharin sodium (0787)

Reaction (b) of sodium prescribed in identification E was not suitable and has been replaced by reaction (a) which gives good results.

Sodium acetate trihydrate (0411)

The title of this monograph was revised to specify the degree of hydration. Since several hydrated forms exist an identification was added to distinguish the different forms.

Sodium benzoate (0123)

Reaction (b) of sodium prescribed in identification B was not suitable and has been replaced by reaction (a) which gives good results.

Sorbitan sesquioleate (1916)

In order to encompass another source, the limits for hydroxyl value and saponification value were modified.

Tobramycin (0645)

This monograph has been revised mainly to replace the TLC in the test for related substances and the microbiological assay by an LC method using amperometric detection, as it has already been proposed for other aminoglycosides.

Triglycerides, medium-chain (0868)

The tests for chromium, copper, lead, nickel and tin were revised in order to use liposoluble reference standards and to avoid phase separation in the reference solutions. The limit for nickel has been increased.

Ubidecarenone (1578)

Taking into account new batch results provided by a manufacturer and new information on the licensed products, the monograph has been revised to set a 0.5 per cent limit for the *cis*-isomer.

Wool alcohols (0593)

The test for peroxide value was adapted to this product.

Wool fat (0134)

In the test for pesticides, chlordane and toxaphene have been deleted from the pesticides to be determined as they are no longer likely to be present in production and are difficult to separate. The test for peroxide value was adapted to this product.

Zinc sulphate heptahydrate (0111)

The title of this monograph has been revised to specify the degree of hydration. Identification test C has been added to distinguish between heptahydrate and hexahydrate.

VACCINES FOR VETERINARY USE

Tetanus vaccine for veterinary use (0697)

The identification section has been modified to give preference to the *in vitro* method and the potency test using toxin neutralisation has been replaced by a serological model.

— PHARMEUROPA — SPECIAL ISSUE —

“List of Standard Terms” 2000 Edition
(21 European Languages)

The present list of Standard Terms is a revised list which was drawn up in response to a request from the European Commission. It covers both medicines for human and veterinary use. Those Standard Terms are to be used in answering the questions 2, 2.1 and 2.2 of part IA, and sections 3 and 6.5 of part IB (Summary of the Product Characteristics) of the EU application format.

The list of Standard Terms is composed of:

— an Introduction:

- a section of general principles and instructions for the use of Standard Terms,
- the summary of the changes (amendments, additions, deletions) performed since the last publication (February 1998),
- procedure for the addition, deletion or modification of terms in the list of Standard Terms,

— three lists of standard terms:

- list of pharmaceutical forms,
- list of routes and/or methods of administration,
- list of containers, closures and administration devices.

The previous edition contained translations in sixteen European languages: Croatian, Danish, Dutch, English, Finnish, French, German, Greek, Italian, Norwegian, Portuguese, Slovak, Slovenian, Spanish, Swedish and Turkish. The present lists have been further enlarged by adding Bulgarian, Czech, Hungarian, Icelandic and Polish Terms.

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