

COMMENTS CONCERNING SOME REVISED/CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 6.5

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the June 2008 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

GENERAL TEXTS

1. General notices

1.1. General statements (conventional terms):

definitions of a number of terms commonly used in monographs and general chapters are included. These definitions are useful additions to aid interpretation of Ph. Eur. texts.

Medicinal product: the definition is that stated in Directives 2001/82/EC (as amended by Directive 2004/28/EC) and 2001/83/EC (as amended by Directive 2004/27/EC).

Excipient: the term 'auxiliary substance' is still mentioned because it is often used in Ph. Eur. monographs.

The definitions have been included in the section Conventional terms. In this context the definitions refer only to terms used in the Ph. Eur. and do not contradict the same terms already defined in national legislation. The definitions will be useful in other fields of activity, for example in anti-counterfeiting documents, since the Council of Europe is wider in geographic scope than the European Union.

Monographs (identification): certain monographs give 2 or more equivalent sets of tests for identification. This concept has been defined and an example is given for illustration. The current system of 1st and 2nd identifications remains. The 2nd identification is for use by pharmacies, and this has been specified.

2.6.12. Microbiological examination of non-sterile products: microbial enumeration tests

Negative control: clarification has been introduced with regard to the performance of negative control. A negative control is to be carried out not only when verifying the performance of the media but also when testing the products.

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

Negative control: clarification has been introduced with regard to the performance of negative control. A negative control is to be carried out not only when verifying the performance of the media but also when testing the products.

Growth promotion and inhibitory properties of the media: *E. coli* has been deleted as an indicative strain for XLD agar since it grows with difficulty on this medium.

Clostridia: the description of the test has been reworded in order to improve internal consistency of the chapter. — Section 4-6-1 reads: "Divide the sample into 2 portions of at least 10 ml". The wording has been included because under 4-6-2 a volume each of the treated and of the untreated sample must be transferred to a container with reinforced medium for clostridia. In order to do this under GLP conditions (e.g. with a

pipette) some excess is necessary.

— A maximum incubation time of 72 h has been added, an incubation time of exactly 48 h being unnecessarily stringent.

— Some concern was raised that facultative anaerobic *Bacillus* species may be confused with *Clostridium* species. In section 4-6-3 it is specified, as in other sections of the chapter, that identification tests must confirm the presence of clostridia, without further specification of those tests.

Recommended solutions and culture media: the statement "Other media may be used if they have similar growth promoting and inhibitory properties" has been reworded because it had been considered misleading. The new wording is "Other media may be used provided that their suitability can be demonstrated".

2.6.24. Avian viral vaccines: tests for extraneous agents in seed lots

Test for avian leucosis viruses. The use of DF-1 cells has been added because, in light of new scientific knowledge, detection of avian leucosis virus in seed lots can be done in DF-1 cells instead of primary or secondary chick embryo fibroblasts. Indeed, the DF-1 cell line supports the growth of subgroups A, B and J of avian leucosis viruses and is resistant to endogenous viruses. Furthermore, this is an improvement of the test, since DEF-1 cells can be obtained easily (for example from ATCC) while there can be supply problems for chick embryo fibroblasts, and the test is less complicated and easier to standardise with no reduction in sensitivity.

2.6.26. Test for anti-D antibodies in human immunoglobulin for intravenous administration

Materials: according to Ph. Eur. policy, reference to Alsever's solution has been deleted and details for the preparation of an appropriate solution are given instead.

2.7.9. Test for Fc function of immunoglobulin

A method performed on microtitre plates has been added as an alternative to the current method using test tubes/cuvettes. This alternative method is more up-to-date and makes it easier to test several samples at the same time. The results obtained using the 2 methods have been shown to be equivalent.

2.7.25. Assay of human plasmin inhibitor

Method: detailed instructions for the reading of the assay have been indicated.

2.9.34. Bulk density and tapped density of powders

Tapped density (Method 3): the text has been modified to correspond to the procedure used in Japan (harmonised text), i.e. 3 determinations are carried out on 3 different samples (using 200 and 400 taps).

5.2.5. Substances of animal origin for the production of immunological veterinary medicinal products

This chapter has undergone a general revision in light of the elaboration of the new chapter *Viral safety (5.1.7)* and the specific needs concerning viral safety for veterinary vaccines.

This revision includes the following principal changes:

— the scope of the chapter is extended to immunological veterinary medicinal products in general;

— risk assessment and risk management are required;
— more details are given in order to clarify the requirements of the source (including species of origin and country of origin of source animals and tissues);
— more details are given regarding validation of the inactivation procedure;
— more details are given regarding the tests for examination of the substance for freedom from extraneous agents, including a general test and specific tests such as a test for pestiviruses.

GENERAL MONOGRAPHS

Substances for pharmaceutical use (2034)

Identification: this section has been modified in accordance with the revised General Notices.

Related substances: the general monograph has been revised in line with the conclusions of the EDQM symposium 'New impurities control: setting specifications for antibiotics and synthetic peptides' held in September 2006; general provisions for the reporting, identification and qualification thresholds applicable to synthetic peptides have been added, and general chapter 5.10. *Control of impurities in substances*

for pharmaceutical use has been modified accordingly; in addition, the thresholds for active substances for veterinary use only have been updated according to the recently revised VICH guideline on impurities in new veterinary drug substances (EMEA/CVMP/VICH/837/99-Rev.1).

Labelling: 'added substance' has been replaced by the term 'excipient', as defined in the revised General Notices published in Supplement 6.5; the last sentence has been deleted since it is covered by the last indent.

VACCINES FOR VETERINARY USE

Infectious chicken anaemia vaccine (live) (2038)

Immunogenicity: it is clarified that egg transmission has to be reduced and that this reduction is demonstrated

indirectly through viraemia and virus excretion in faeces; the dates for collecting faecal samples have been changed since the virus is excreted later in faeces than in blood.

HOMOEOPATHIC PREPARATIONS

Herbal drugs for homoeopathic preparations (2045)

Foreign matter: since the limit of 2 per cent *m/m* has been removed from chapter 2.8.2, this limit has to be

introduced into the general monograph on herbal drugs for homoeopathic preparations, as has been done for the general monograph *Herbal drugs (1433)*.

MONOGRAPHS

Aceclofenac (1281)

Related substances: in order to facilitate unambiguous peak identification of impurities B, C, D, E and G, reference solution (g) including a CRS spiked with impurities B, C, D, E and G has been added. Relative retentions have been slightly modified based on experimental data.

Benzyl alcohol (0256)

Related substances: the test description has been changed to deal with cases where the substance contains any peaks that overlap with the peaks due to ethylbenzene or dicyclohexyl; precise instructions have been added on how to correct for these additional peaks when calculating the sums and the disregard limit.

Buprenorphine (1180)

Identification A: replacement of the IR reference spectrum by a CRS in accordance with current policy.
Related substances: isocratic LC replaced by gradient LC covering additional impurities F, G, H, I and J.
Assay: previous method gave results above the upper limit and has therefore been revised.

Buprenorphine hydrochloride (1181)

Identification A: replacement of the IR reference spectrum by a CRS in accordance with current policy.
Related substances: isocratic LC replaced by gradient LC covering additional impurities D, E, F, G, H, I and J.
Assay: previous method gave results above the upper limit, and has therefore been revised.

Caffeine monohydrate (0268)

Related substances: TLC replaced by LC in accordance with current policy.
Impurities: addition of other detectable impurities D, E and F.

Carboplatin (1081)

Solution S2: as a consequence of the deletion of the test for heavy metals, solution S2 is deleted and a specific description of the solution to be used in the test for chlorides is introduced.
Heavy metals: the test is deleted as a specific test for silver is part of the monograph.

Ceftazidime pentahydrate (1405)

Title: the degree of hydration has been added in order

to harmonise with the new monograph *Ceftazidime pentahydrate with sodium carbonate for injection* (2344).

Definition: semi-synthetic origin from a fermentation product has been added.

Related Substances: TLC replaced by LC in accordance with current policy; limits harmonised with those proposed in the new monograph *Ceftazidime pentahydrate with sodium carbonate for injection* (2344).

Impurities: addition of specified impurity G and other detectable impurity H, and deletion of impurity D as it is no longer detected in batches.

Heavy metals: test added.

Cyproheptadine hydrochloride (0817)

Identification: series of identification tests simplified.

Related substances: TLC replaced by LC in accordance with current policy.

Impurities: addition of specified impurity C; structure of impurity B (dibenzosuberone) corrected.

Desmopressin (0712)

Labelling: statement added on the suitability of the substance for use in the manufacture of parenteral preparations.

Impurities: section added describing unspecified impurities controlled by LC.

Dimenhydrinate (0601)

Related substances: TLC replaced by LC in accordance with current policy.

Heavy metals: test deleted in accordance with technical guide recommendations.

Impurities: section added describing impurities controlled by LC.

Etacrynic acid (0457)

Identification C: sample preparation deleted.

Related substances: TLC replaced by LC, in accordance with current policy.

Impurities: section added describing impurities controlled by LC.

Frangula bark dry extract, standardised (1214)

Production: to cover all licensed products on the European market, the range of the production solvent has been widened from ethanol (50-80 per cent V/V) to ethanol (50-90 per cent V/V).

Ginkgo leaf (1828)

Identification B: illustration of the powdered herbal drug added.

Guaiacol (1978)

Impurity A: impurity C, controlled by the GC test, is also detected by the current LC method at about 78 min; a gradient step has been added to elute impurity C before the subsequent analysis starts.

Related substances: conditions have been modified to avoid possible co-elution of impurities B and E.

Assay: test solution (b) and reference solution (c) have been made 10 times more dilute to obtain sharper peaks.

Impurities: other detectable impurities F, G and H have been added.

Hydrocortisone (0335)

Identification: TLC of test B replaced by a cross-reference to the LC test for related substances, to avoid the use of ether.

Specific optical rotation: dioxan replaced by the less-toxic solvent methanol.

Related substances: method revised to control a larger spectrum of impurities and limits updated based on current batch data.

Impurities: list updated based on current batch data.

Lactose, anhydrous (1061)

Acidity or alkalinity: a more concentrated phenolphthalein solution is used. To avoid problems of interpretation, the indicator colour to be obtained is described as 'pink or red'. The revision has been agreed by the PDG (Pharmacopoeial Discussion Group) within the framework of international harmonisation.

Lactose monohydrate (0187)

Acidity or alkalinity: a more concentrated phenolphthalein solution is used. To avoid problems of interpretation, the indicator colour to be obtained is described as 'pink or red'. The revision has been agreed by the PDG (Pharmacopoeial Discussion Group) within the framework of international harmonisation.

Magnesium stearate (0229)

This text has been revised to reflect the changes following the international harmonisation of the monograph.

Definition: wording revised.

Identification: identification D test replaced.

Solution S: *distilled water R* replaced by *water R*.

Acidity or alkalinity: small changes.

Chlorides, sulphates: Ph. Eur. general methods replaced.

Cadmium, lead, nickel: several changes in description of method and preparation of solutions.

Assay: fatty acid composition test renamed 'stearic acid and palmitic acid'; repeatability criteria added.

Maltodextrin (1542)

Definition: substances with a degree of hydrolysis of 20 have been excluded as they are under the scope of the monographs *Liquid glucose* (1330) and *Spray-dried liquid glucose* (1525); this is in line with the specification of maltodextrin in the Food Chemical Codex and in the USP-NF.

Methyldopa (0045)

Identification: the 2nd identification has been deleted to avoid the use of pyridine and as the substance is used neither in pharmacies nor in hospitals. 2 alternative identifications are given; presence of the correct enantiomer can be verified by the specific optical rotation (previously given as a test for optical rotation) or by the test for enantiomeric purity; 1 of these tests is to be carried out together with the usual IR identification.

Optical rotation: this test has been transferred to the Identification section as an LC method for enantiomeric purity has been introduced.

Related substances: the TLC for methoxymethyldopa and related substances has been replaced by an LC for related substances in accordance with current policy.

Enantiomeric purity: the former test for optical rotation has been replaced by an LC test in accordance with current policy.

Assay: the assay has been modified to use a titration with detection of the end-point by potentiometry.

Impurities: a section describing the impurities controlled by LC has been added.

Methylethylamine maleate (1788)

Related substances: an isocratic phase has been added to the gradient, the normalisation procedure has been replaced by external standardisation, and limits for the specified impurities and the total have been tightened.

Mirtazapine (2338)

Related substances: the retention time of mirtazapine has been amended in view of the new column recommended in the knowledge database; a higher value for the symmetry factor has been authorised.

Oxolinic acid (1353)

Related substances: in order to enhance the detection of the spot due to impurity B, the concentrations of the test solution and reference solutions (a) and (b) have been increased; the use of a plate 'with a particle size of narrow distribution' is no longer prescribed.

Paraffin, white soft (1799)

Polycyclic aromatic hydrocarbons: the limit of 300 ppm mentioned in the monograph reflected the naphthalene concentration of the reference solution; the absorbance of the test solution (extraction in dimethyl sulfoxide) must not exceed the absorbance of the reference solution. The number, 300 ppm, could not be translated into a concentration of polycyclic aromatic hydrocarbons but is a concentration of naphthalene. The concentration of polycyclic aromatic hydrocarbons in white soft paraffin is actually much lower. It was an incorrect indication that caused confusion for the producers and users. The indication of a maximum of 300 ppm has therefore been deleted in the monograph.

Penicillamine (0566)

Impurity A: chromatographic conditions modified (column dimensions, flow rate, injection volume); addition of a system suitability test; introduction of a statement on the use of freshly prepared solutions.

Pentaerythryl tetranitrate, diluted (1355)

Related substances: limit for specified impurity D widened to 0.3 per cent based on approved specifications.

Polysorbate 80 (0428)

This text has been revised to reflect the changes following the international harmonisation of the monograph.

Characters: the appearance of the product has been changed.

Ethylene oxide and dioxan: a more user-friendly method using a commercially available solution of ethylene oxide has been introduced.

Povidone (0685)

This text has been revised to reflect the changes following the international harmonisation of the monograph. Corrections of the expression of some sample sizes and volumes have been made.

Peroxides: the test solution and the compensation liquid are prepared with an amount of povidone calculated on the anhydrous basis.

Formic acid: a better description of the column used for the preparation of the test solution is included.

Pyrrolidone (2180)

Related substances: limits have been widened for specified impurities and for the total. A reference solution has been added for identification of impurities A and B.

Red poppy petals (1881)

Identification B: illustration of powdered herbal drug added.

Sodium picosulfate (1031)

Identification A: method of sample preparation no longer specified.

Solution S: carbon dioxide-free water is used.

Related substances: TLC replaced by LC in accordance with current policy; impurity C added under Other detectable impurities.

Heavy metals: the test is not of practical relevance for the substance and is therefore deleted.

Stearic acid (1474)

This text has been revised to reflect the changes following the international harmonisation of the monograph.

Assay: a requirement for relative standard deviation has been added.

Nickel (non-harmonised test): method 2.4.31 has been included because method 2.4.27 is not suitable for fatty acids; severe problems such as an explosion were reported with the latter method.

Sucrose monopalmitate (2319)

Free sucrose: an error had been reported regarding the concentration of reference solution (a), the concentration has been increased to 0.2 mg/ml.

Sucrose stearate (2318)

A 3rd grade is present on the market and is now included in the scope of the monograph. It only differs from the other 2 grades in its composition of mono-, di-, tri- and polyesters.

Free sucrose: an error had been reported regarding the concentration of reference solution (a); the concentration has been increased to 0.2 mg/ml.

Tenoxicam (1156)

Related substances: TLC replaced by LC in accordance with current policy.

Impurities: section updated.

Tolnaftate (1158)

Identification: the series of identification tests has been simplified since the substance is not used in pharmacies. **Appearance of solution:** this test has been deleted as the substance is for external use.

Impurity D: additional LC test introduced to detect N,3-dimethylaniline.

Related substances: TLC replaced by LC in accordance with current policy.

Zidovudine (1059)

Related substances: based on several EDQM laboratory reports the resolution criterion has been tightened in test B from minimum 1.0 to minimum 1.5 in order to ensure baseline separation.