COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 4.8

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the June 2003 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

2.2.32. Loss on drying

There is a difference between the Ph. Eur., JP and USP regarding the drying temperature. JP and USP generally prescribe 105 ± 2 °C, whereas Ph. Eur. has 100-105 °C. Enquiries were made with pharmaceutical manufacturers to see whether harmonisation of the conditions with those of JP and USP would imply an unnecessary burden in terms of requalification of equipment. The replies received indicated that industry would welcome an alignment of the drying conditions of the 3 pharmacopoeias, particularly for harmonised monographs. The general method has therefore been revised to introduce a general tolerance of ± 2 °C for the drying temperature indicated in monographs. Future harmonised monographs can then prescribe a drying temperature of 105 °C, as in JP and USP. This will also deal with one of the questions regularly submitted to the Secretariat regarding the acceptable tolerance for those monographs where drying is carried out at a temperature indicated by a single value (for example, 60 °C). It is not proposed at this stage to make a general change to existing monographs where 100-105 °C is indicated.

MONOGRAPHS

Allopurinol (0576)

The gradient LC in the test for related substances has been replaced by 2 different isocratic LC methods which allow better control of the impurities.

Anise oil (0804)
Star anise oil (2108)

It is more appropriate to have separate monographs for anise oil and star anise oil instead of a single monograph covering both oils.

The TLC identification has been revised to replace the vanillin spray reagent by methyl 4-acetylbenzoate, which is more efficient.

Tests for the absence of foeniculin and fenchone (in the case of anise oil) and for the absence of fenchone and pseudoioseugenyl 2-methylbutyrate (in the case of star anise oil) have been introduced in order to distinguish the 2 oils from each other.

Bromhexine hydrochloride (0706)

A test for appearance of solution has been introduced as this compound can be used for injections.

Clonazepam (0890)

As for the other revised benzodiazepine monographs, the identification has been simplified because IR alone is sufficient. Based on the daily dose, the test for heavy metals has been deleted.

Codeine phosphate hemihydrate (0074)
Codeine phosphate sesquihydrate (0075)

A cross-reference to the test for loss on drying has been added under Identification to differentiate codeine phosphate hemihydrate from the sesquihydrate.

Dithranol (1007)

The preparation of the solutions in test B for related substances has been modified following dissolution problems.

Edetic acid (1612)

The test for impurity A has been replaced by the same test used in sodium calcium edetate (0231) and disodium edetate (0232).

Estradiol hemihydrate (0821)

The limits in the test for related substances have been modified. Indeed, due to the introduction of estradiol for peak identification CRS (containing impurities A, B and C) and of an *in situ* oxidation to produce impurity D, it has become possible to tighten the limits for the impurities and better reflect the quality of the licensed products.

Flumazenil (1326)

The LC used in the test for related substances has been revised to detect a larger range of potential impurities. The limit for individual impurities has been tightened in accordance with the quality of the marketed product.

Histidine (0911)

The mean optical rotation observed for a very pure substance is 11.9 whereas the monograph limits were 11.8 to 12.8. A range of 11.4 to 12.4 has therefore been defined to reflect this mean value.

Human plasma (pooled and treated for virus inactivation) (1646)

In the production section, a test for B19 virus by nucleic acid amplification techniques to reduce the B19 DNA virus level to 10^4 IU/ml in plasma pools before the application of the virus inactivation/removal process has been added.

An assay for coagulation factor XI with a minimum limit of 0.5 units/ml has been added because the product may be used for the treatment of factor XI deficiency.

Leuprorelin (1442)

In the test for related substances the calculations using an external standard and the normalisation procedure give identical results. Therefore the test has been simplified by using the normalisation procedure.

Reference to the general chapter on amino acid analysis (2.2.56) has been made and the test is now considered as an identity test.

Mexiletine hydrochloride (1029)

In the tests for impurity D and for related substances the reference solutions have been modified following the establishment of mexiletine impurity D CRS and mexiletine impurity C CRS.

Nifuroxazide (1999)

The test for related substances has been revised to take into account the solubility problems reported.

Omeprazole (0942)

In the test for residual solvents the limit for one of the solvents has been deleted as it was less strict than the one prescribed in general chapter 5.4.

Ribwort plantain (1884)

The definition and identification of the drug have been revised in order to include the scape. This modification allows the foreign matter section to remain unchanged.

Sodium glycerophosphate, hydrated (1995)

The assay method in this monograph showed a systematic bias which was not taken into account in the limits of the assay (results almost systematically greater than the upper limit). When the results of the assay are corrected using the result of the test for alkalinity (for which the limit of 1 ml corresponds to 3.1 per cent of sodium glycerophosphate), the observed values comply with the prescribed limits.

Sorbitol, liquid, partially dehydrated (2048)

The maximum difference authorised between the contents found and the contents stated on the label (nominal values) has been widened to take into account the reproducibility of the method used for the assay. It has also been clearly defined which limits apply to the nominal values and which limits apply to the values found by the user.

Sucrose (0204)

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

The tests for absorbance, for sulphite and for lead are based on methods from ICUMSA (International Commission for Uniform Methods of Sugar Analysis).

Temazepam (0954)

In the test for related substances the TLC has been replaced by an LC method. A separate test for absorbance has been introduced to control impurity A. The absorbance limit proposed corresponds to a content of 0.05 per cent. Nevertheless, a gradient has been introduced under related substances to ensure the elution of this late eluting impurity A.

Testosterone (1373)

In the test for related substances the TLC has been replaced by an LC and another TLC method to cover 8 additional impurities (C to J). 8 impurities are detected by LC at 254 nm. Impurities D and F, due to their poor absorbance at 254 nm, are detected by the new TLC method.

Water for injections (0169)

The analytical method in the conductivity section has been amended:

— to also enable in-line monitoring of conductivity at normal or elevated temperatures,

— to take account of factors (CO_2, absorption, fluctuations in pH) with a potential impact on analytical results which might lead to unjustified out-of-specification decisions at the very low conductivity specification level (maximum 1.1 $\mu S \cdot cm^{-1}$ at 20 °C).

This procedure is similar to that in the USP monograph on Water for injections.

In addition, the conductivity section under Sterilised water for injections has been amended with regard to details on equipment to be used in the conductivity determination for sterilised water for injections in containers.

No changes were made with regard to the valid conductivity specifications.

The tests to be performed are integrated into the body of the monograph, without cross-reference to the monograph on Purified water (0008).

Water, highly purified (1927)

The analytical method in the conductivity section has been amended:

— to also enable in-line monitoring of conductivity at normal or elevated temperatures,

— to take account of factors (CO_2, absorption, fluctuations in pH) with a potential impact on analytical results which might lead to unjustified out-of-specification decisions at the very low conductivity specification level (maximum 1.1 $\mu S \cdot cm^{-1}$ at 20 °C).

This procedure is similar to that in the USP monograph on Water for injections.

No changes were made with regard to the valid conductivity specifications.

Water, purified (0008)

The analytical method in the conductivity section under Purified water in bulk has been amended to also enable in-line monitoring of conductivity at normal or elevated temperatures.

The data points in Table 0008.-1 have been calculated on the basis of the USP sodium chloride model and the conductivity data in the Stage 1 table of USP General Method 645 - Water conductivity.

Reverse osmosis and ion exchange by means of resins are today used as a rule for the preparation of purified water. These techniques hardly lead to water temperatures of more than 40 °C; Table 0008.-1 could therefore be restricted to temperatures of up to 50 °C. However, it appears that in some countries purified water is also produced by means of distillation. For this reason the table has been extended to 100 °C. Requirements in the temperature range from 75 °C to 90 °C do not differ, which concurs with the USP Stage 1 data. Exact calculation on the basis of the USP Stage 1 data and the relevant data for water density and ion product even show a slight depression of results in this range.

Compared to Water for injections, conductivity requirements for Purified water are less stringent (1.1 $\mu S \cdot cm^{-1}$ versus 4.3 $\mu S \cdot cm^{-1}$ at 20 °C). This permits restriction of the conductivity measurement of Purified water to a less complicated one stage measurement procedure. This is supported by practical experience gained with this limit (maximum 4.3 $\mu S \cdot cm^{-1}$ at 20 °C), valid since 1 July 1999.

Reverse osmosis has been added as a production method.

RADIOPHARMACEUTICAL PREPARATIONS

Sodium iodide (^{123}I) injection (0563)

The title of the monograph has been changed to indicate the use of the product and to distinguish it from sodium iodide (^{123}I) solution, which can be used for labelling. In the definition the requirement for the specific activity has been deleted since the described method of production results in a solution of iodide-123 without added carrier iodide which is appropriate for the intended use of the product. In the radiochemical purity determination, the paper chromatographic procedure has been replaced by an LC procedure (in line with the other radiopharmaceutical iodine preparations) which is quicker to use.

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