

COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN THE 5th EDITION

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the November 2003 session. This information completes the modifications indicated by lines in the margin. Hence, the information below is not necessarily exhaustive.

ANALYTICAL METHODS

2.2.1. Clarity and degree of opalescence of liquids

Instrumental methods for the determination of clarity and degree of opalescence of liquids are alternative methods that may be used after verification using the Ph. Eur. reference standards as described. They do not replace the existing visual method of the Pharmacopoeia.

Regarding the instrument specifications; the use of instruments with other specifications is not excluded, but they have to be validated and shown suitable for the particular intended purpose.

2.2.3. Potentiometric determination of pH

Changes have been made to the drying conditions for the substances used in preparation of standard solutions, to align with recommendations from standardisation bodies and the practice of reagent suppliers. An additional standard solution has been included for the upper values of pH, since this was not covered by the previous solutions.

Although the general chapter is not on the programme of harmonisation with the USP and the JP, the changes made will remove some minor differences between the general chapters of the pharmacopoeias and improve the present chapter of the Ph. Eur.

2.2.5. Relative density

The scope of the chapter has been extended to cover density meters based on an oscillating transducer that are commonly used for density measurements in pharmaceutical analysis.

2.2.24. Absorption spectrophotometry, infrared

The general chapter has been adapted to the current generation of Fourier-transform infrared (FT-IR) spectrophotometers. FT-IR instruments use a polychromatic light source and have a data processing system for converting the interferogram produced to an absorption/transmission spectrum by a mathematical function known as Fourier transformation. Controls applied to monochromator instruments are not always valid for FT-IR instruments, where resolution is influenced largely by the instrument parameters chosen. The resolution and the wave-number scale may be checked using a polystyrene film but the resolution requirement is better expressed in terms of differences in absorbance rather than transmission. A stricter tolerance on the accuracy of the wave-number scale has been prescribed since FT-IR instruments have an internal laser calibrator and software that provide high wave-number accuracy.

For identification by reference spectra, criteria for FT-IR instruments have been introduced to reflect their superior performance.

The thickness of the polystyrene film used for calibration has been changed from 0.05 mm to 0.04 mm, to

align with the films supplied by standards institutes and instrument suppliers, which are stated to have a thickness of about 35 μm . This value has been included.

2.2.34. Thermal analysis

The general chapter Thermogravimetry (2.2.34), renamed Thermal analysis has been supplemented by the addition of sections on differential scanning calorimetry and thermomicroscopy.

2.2.40. Near-infrared spectrophotometry

The chapter has been revised to include the current technical and scientific developments and advances in near-infrared (NIR) spectrophotometry. Application of NIR in quantitative determinations, has been made and validation parameters, both for qualitative and quantitative analysis, have been included.

2.4.8. Heavy metals

1. A new method (G) has been added for use where method A or B cannot be applied. Methods C, D and F which were used for such substances all have more or less serious drawbacks; methods C and D require ignition at up to 800 °C leading to loss of analyte in varying degrees. Although this is countered by treatment of the standard in the same conditions, the robustness of the methods is not optimal. Method F (identical to method II of USP) avoids loss of analyte by use of wet digestion but is fastidious and time-consuming (a day and a half is required for each test). Method G uses microwave-assisted wet digestion and has been found satisfactory with a range of substances, which were tested by methods C, D or F.

2. A monitor preparation has been added to methods C, D and F as a control for each test. This type of control is useful for the heavy metals test where the sample preparation is not by simple dissolution.

3. An option for filtration has been added to methods A, B, C, D and F (using the filter at present prescribed for method E but omitting the prefilter). Where a test result is difficult to interpret filtration provides a more easily read result in the form of a dark spot on the filter membrane. This option also provides a means of obtaining a permanent record of the result.

4. The use of sodium sulphide solution as an alternative to thioacetamide reagent has been included. A monitor solution is to be included also for methods A and B if sodium sulphide solution is used.

2.6.9. Abnormal toxicity

The test for abnormal toxicity of immunosera and vaccines for veterinary use has been deleted since it is no longer the policy of the Commission to use this animal test.

2.6.14. Bacterial endotoxins

The general monograph on *parenteral preparations (0520)* has been modified to require application of the test for bacterial endotoxins for all products, irrespective of the dose volume (except for veterinary products, where a threshold is maintained). Therefore, the test is required for products administered intramuscularly or subcutaneously (and by other parenteral routes).

Further, a cross-reference has been made to the general chapter on bacterial endotoxins to direct users to the guidance section on determination of acceptance criteria for products on the route of administration. The intravenous and intrathecal routes are at present covered by the general chapter but no guidance is given for other routes.

The level of bacterial endotoxins in small-volume parenterals is essentially used as a quality criterion for monitoring of the manufacturing process, rather than from safety concerns. The acceptance criteria are therefore determined on results obtained during the development of the product.

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

2.6.25. Avian live virus vaccines: tests for extraneous agents in batches of finished product

General chapters 2.6.3, 2.6.4, 2.6.5 and 2.6.6 have been restructured and have been renumbered 2.6.24 and 2.6.25. For tests applied to each batch of vaccine, the test in chicks has been replaced by a series of tests in cell cultures and a third route of administration in the test in embryonated eggs (inoculation into the yolk sac) has been added. This new testing scheme will lead to a considerable reduction of the number of animals needed for routine testing while maintaining the guarantee of freedom from extraneous agents. This change is part of the action of the European Pharmacopoeia Commission as a consequence of the European Convention on the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.

2.7.16. Assay of pertussis vaccine (acellular)

To harmonise requirements on age limit for mice used in potency assays, "about 5 weeks old" has been specified.

3.2.1. Glass containers for pharmaceutical use

For more than 50 years it has been known that alkaline or neutral preparations for parenteral use may affect the inner surface of glass containers. A small amount

of alkali may be leached and can cause a change in the composition of the preparation. The intensity of the attack in comparable conditions depends on the nature of the product, and the composition of the glass type used for manufacturing the containers.

The last edition of the European Pharmacopoeia prescribed 2 tests for the classification of glass used in glass containers. The glass-grain test gives sufficient information on the glass as a material but inadequate information about what happens to the inner surface of the glass in contact with the solution. For this reason the hydrolytic surface test has been developed. The release of alkali from the glass surface is determined by titration as a mean value of a number of containers. This test can be done in laboratories with common equipment. The disadvantage is that there is no information about the standard deviation concerning the results of the single containers and no information about outliers.

In addition to the general chapter there are the following ISO standards:

ISO 720 - Glass-Hydrolytic resistance of glass grains at 121 °C.

ISO 4802 - Glassware-Hydrolytic resistance of the interior surfaces of glass containers:

Part 1: Determination by titration.

Part 2: Determination by flame spectrometry.

These standards are mainly based on the work of Technical Committee 2 of the International Commission on Glass (ICG). Recent studies and laboratory intercomparisons have shown that the results obtained using the titrimetric or the flame spectrometry method are not always comparable. Both methods cannot be considered equivalent nor interchangeable.

It has therefore been decided to keep the current titrimetric method as the official method but describe the flame spectrometry method in an annex to this chapter and restrict its use to specific cases.

In view of the fact that some reagents in the test for arsenic are rather toxic it was decided to replace the test by Atomic Absorption Spectrometry.

As the present method of measuring the light transmission is not very precise due to the scattering of the light on the glass surface it has been proposed to use a UV-VIS spectrophotometer equipped with a photodiode detector or equipped with a photomultiplier tube coupled with an integrating sphere.

MONOGRAPHS

Adrenaline tartrate (0254)

The reagent Diethoxytetrahydrofuran used in identification E is no longer available. The second identification series has been deleted.

Ammonium glycyrrhizate (1772)

The substance is hygroscopic, therefore the limit for water has been increased to 6.0 per cent.

Buserelin (1077)

In the test for amino acid analysis reference has been made to the general chapter on amino acid analysis and the test is now considered as an identity test.

A section on impurities has been added.

Cefapirin sodium (1650)

A test for appearance of solution has been introduced because the substance is used parenterally.

Codergocrine mesilate (2060)

A production section has been added that is the same as for other current monographs on mesilate salts.

Dexpanthenol (0761)

Dexpanthenol CRS, a 5.0 per cent *m/V* solution in ethanol has been replaced by a CRS produced by evaporation. The monograph has been revised accordingly.

Doxycycline hyclate (0272)

The method for ethanol determination as published in the 4th Edition of the Ph. Eur. has been reintroduced because the general method used gave poor reproducibility for the calculation of ethanol content.

Epirubicin hydrochloride (1590)

Epirubicin impurity A (doxorubicinone) is no longer available as a CRS and is now obtained by *in situ* degradation (second most abundant peak).

A correction factor has been introduced because quantification is no longer performed against the CRS but instead using a dilution of the test solution.

Estradiol benzoate (0139)

Based on the information submitted by a manufacturer, a correction factor applying to impurity C has been added.

Etilefrine hydrochloride (1205)

Stability problems with impurity A in reference solution (b) for the test for related substances were observed during the experimental studies performed for a Proficiency Testing Study (PTS). A warning has therefore been introduced to prescribe the preparation of the solutions immediately before use.

Famotidine (1012)

The TLC for related substances has been replaced by an LC that allows better control of the impurities. The correction factors given take into account the variations in sensitivity due to absorption differences and the flow rate gradient. For the unknown impurities, the lowest sensitivity due to the highest flow rate has also been taken into account for the impurities eluting after 25 minutes.

Goserelin (1636)

In the test for amino acid analysis reference has been made to the general chapter on amino acid analysis and the test is now considered as an identity test.

A section on impurities has been added.

Human anti-D immunoglobulin (0557)

A minor revision of the monograph is presented to align it with the intravenous product regarding the requirements for hepatitis b virus antibodies; a waiver to the requirement for a minimum level of hepatitis B virus antibodies has been made, subject to assessment of the virus inactivation procedure by the competent authority.

Insulin, human (0838)

With the introduction of the monographs on insulin analogues, *insulin aspart (2084)* and *insulin lispro (2085)* the monograph has been revised as follows:

- The limit of 10ppm for host-cell-derived proteins was considered inappropriate in the absence of a prescribed method, therefore the limit has been changed and must be approved by the competent authority.
- Human insulin is produced via a single chain precursor that is not always human proinsulin. Consequently, a test for single chain precursor, whose limit must be approved by the competent authority, has been introduced in the production section.
- Routine testing of proinsuline-like immunoreactivity has been restricted to human insulin produced by enzymatic modification of porcine insulin.

Iohexol (1114)

The monograph has been revised to:

- comply with the requirements of chapter 5.4 on residual solvents, which applies in a general manner, therefore the specific test in the monograph has been deleted,
- add 5 new impurities,
- modify the limits in the test for related substances and some other tests, based on batch results,
- harmonise the assay with the USP.

Iopamidol (1115)

The test for related substances has been revised to cover 4 additional impurities.

Ketoprofen (0922)

5 additional impurities have been added and the relative retentions (unadjusted) of all impurities have been introduced.

Lactose, anhydrous (1061)

Tests for functionality-related characteristics have been introduced.

The test for the ratio of α -lactose and β -lactose, and for loss on drying at 80 °C have been moved from the tests section to the functionality-related characteristics section of the monograph and therefore the limit for loss on drying has been deleted.

Paraffin, light liquid (0240)**Paraffin, liquid (0239)**

The evaluation of the upper layer has been deleted from the test for readily carbonisable substances because regular batches (mainly highly viscose liquid paraffin) failed the test as the colour obtained was too weak.

Povidone, iodinated (1142)

The production section has been revised to allow the use of povidone containing up to 8.0 per cent of water as precursor, in order to produce a more stable product (i.e. containing 7-8 per cent moisture and therefore less friable); the monograph stated that iodinated povidone had to be made from precursor material meeting the requirements of the povidone monograph, which allowed up to 5.0 per cent of water.

Primidone (0584)

A test for related substances by LC has been introduced together with the corresponding impurities list. The test for water-soluble substances absorbing ultraviolet light is therefore no longer necessary and has been deleted.

The column used is not a classical one but it allows higher flow rates than usual columns and thus has the advantage of giving sharper peaks and considerably shortening the analysis time.

Propyl gallate (1039)

The precision of the assay was not satisfactory so it has been replaced by a UV-spectrophotometric assay to harmonise with the new monographs on Octyl gallate and Dodecyl gallate,

Propylene glycol (0430)

The range has been widened in the limits for identification D because products on the market did not

always fulfil the limits but tended to show results lower than 123° C.

Protirelin (1144)

A section on impurities has been added. In this context the use of a leaflet in the system suitability test is no longer necessary.

Risperidone (1559)

Risperidone for system suitability CRS containing the 5 specified impurities (A to E) at about 0.2 per cent has been introduced in the LC method in order to identify

their peaks. Relative retentions have been added to the monograph. The resolution test between risperidone/haloperidol has been replaced by a peak-to-valley-ratio between the peaks due to impurity D and risperidone.

Sulfamethoxazole (0108)

The test for related substances has been revised. The new isocratic method allows the separation of 6 impurities (A-F) that have been introduced.

A test for clarity has been introduced under Appearance of solution as the substance can be used in parenteral dosage forms.

VACCINES FOR HUMAN USE

Diphtheria and tetanus vaccine (adsorbed) (0444) Diphtheria, tetanus and pertussis vaccine (adsorbed) (0445) Diphtheria vaccine (adsorbed) (0443)

To harmonise the requirement for free formaldehyde content in monographs for diphtheria and/or tetanus vaccines, the free formaldehyde content can also be determined on the bulk-purified antigens.

Diphtheria, tetanus and hepatitis B (rDNA) vaccine (adsorbed) (2062)

In accordance with established policy, the test for abnormal toxicity has been deleted as it has been replaced by the specific toxicity of the diphtheria and tetanus components.

Diphtheria, tetanus, pertussis and poliomyelitis (inactivated) vaccine (adsorbed) (2061) Diphtheria, tetanus, pertussis, poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2066)

In accordance with established policy, the test for abnormal toxicity has been deleted since there is a test for the specific toxicity of the diphtheria and tetanus components and an animal test under 'Tests'.

Diphtheria vaccine (adsorbed) for adults and adolescents (0646) Diphtheria and tetanus vaccine (adsorbed) for adults and adolescents (0647)

To harmonise the requirement for free formaldehyde content in monographs for diphtheria and/or tetanus vaccines, the free formaldehyde content can also be determined on the bulk-purified toxoids.

Haemophilus type b conjugate vaccine (1219) Meningococcal polysaccharide vaccine (0250) Typhoid polysaccharide vaccine (1160)

To harmonise monographs, the test is carried out for purity of bacterial vaccines on harvests and seed lots. To take into account current practice as regards the purity of harvests and seed lots, there is no need to count 10 000 organisms.

Tetanus vaccine (adsorbed) (0452)

To harmonise the requirement for free formaldehyde content in monographs for diphtheria and/or tetanus vaccines, the free formaldehyde content can also be determined on the bulk-purified toxoids.

VACCINES FOR VETERINARY USE

Avian infectious bronchitis vaccine (live) (0442) Avian infectious bursal disease vaccine (live) (0587) Avian infectious encephalomyelitis vaccine (live) (0588) Avian infectious laryngotracheitis vaccine (live) (1068) Duck viral hepatitis type I vaccine (live) (1315) Fowl-pox vaccine (live) (0649) Marek's disease vaccine (live) (0589) Newcastle disease vaccine (live) (0450)

All monographs on avian live virus vaccines have been entirely revised. This revision covers a variety of issues:

- addition or completion of the Production section where it is absent or insufficient in the monographs;
- in the Definition section, inclusion of a statement of the scope of the monograph in terms of the indications for use;
- a change in approach for the tests for extraneous agents; the monographs allowed omission of certain tests at the discretion of the competent authority whereas the revised monographs give a series of tests to be carried out on the seed lot and an

abridged series to be carried out on each production batch, without leaving discretion in the tests to be applied; this approach leads to better harmonisation of the standards for avian vaccines;

- a new presentation for the monographs has been used that is very different from that used previously; this presentation is intended to clarify issues that have been raised by users; it is intended to apply this presentation to all monographs on veterinary vaccines.

Canine leptospirosis vaccine (inactivated) (0447)

Together with the elaboration of a monograph on Bovine leptospirosis vaccine (inactivated) (1939), the current monograph on Canine leptospirosis vaccine (inactivated) (0447) has been updated extensively, notably to complement the Production section and to add a potency test in dogs. The batch potency test has been modified to include the possibility of using a serological model or an in vitro test (for vaccines without an adjuvant). The proceedings of the EDQM symposium on leptospira vaccines (March 1999) give background information on these changes (Pharmeuropa Bio 99-2).