

## COMMENTS CONCERNING SOME REVISED/CORRECTED TEXTS PUBLISHED IN THE SUPPLEMENT 6.2

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the June 2007 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.

### GENERAL TEXTS

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

Because some blood groups are rare in some countries, which leads to supply difficulties, requirements have been modified regarding the supply of:

- D-positive red blood cells (in addition to OR<sub>2</sub>R<sub>2</sub> donors, the use of OR<sub>1</sub>R<sub>1</sub> and OR<sub>1</sub>R<sub>2</sub> donors is now allowed, although OR<sub>2</sub>R<sub>2</sub> donors are preferred) and;
- D-negative red blood cells (a single Orr donor is now allowed, although the use of 3 Orr donors is preferred).

Furthermore, clarification is given regarding:

- the use of sodium azide in the PBS buffer used to prepare the reference and test solutions;
- the calculation of titres of the preparation to be examined and the reference preparation at an IgG concentration of 25 g/l; a nominal 2-fold dilution factor is assigned to these 25 g/l solutions in order to allow comparison of both preparations;
- the introduction of requirements regarding the negative control preparation.

#### 2.8.13. Pesticide residues

This general chapter has been revised for the following reasons:

- to take account of the regulation EU 396/2005 replacing directives EC 76/895 and EC 90/642;

– to extend the list of pesticides frequently observed in herbal drugs;

– to limit the pesticides in view of toxicology data and according to a 90 percentile approach;

– to modify the formula for the calculation of the limit for the pesticide content in extracts and other pharmaceutical forms prepared from herbal drugs;

– to give more details on the validation procedure for a chosen analytical method;

– to delete the method for the determination of pesticides in herbal drugs, which was given for information; this method was misinterpreted as a reference method.

#### 2.9.9. Measurement of consistency by penetrometry

**Apparatus:** revised to take account of the specifications of the cone (Figure 2.9.9.-2) mentioned in ASTM standard D217-02.

#### 2.9.23. Gas pycnometric density of solids

General revision due to international harmonisation of the text.

#### 2.9.38. Particle-size distribution estimation by analytical sieving

**Test sieves:** the unit used for the recommended USP sieves has been corrected from mesh to micrometres.

## VACCINES FOR VETERINARY USE

#### Furunculosis vaccine (inactivated, oil-adjuvanted, injectable) for salmonids (1521)

Since additional experience has been gained with fish vaccines in the last few years, the development safety studies are performed on 1 batch of vaccine instead of 3. For other veterinary vaccines, development safety studies are always required only on 1 batch of vaccine. Furthermore, this proposal is in line with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.

#### Swine-fever vaccine (live, prepared in cell cultures), classical (0065)

Since the Epidemiological situation and the disease control strategies in Europe have changed, routine vaccination has not been used for more than 10 years. It has nevertheless been decided to revise the monograph to bring it into line with current concepts since member states may choose to use the vaccine for disease control if there is a widespread outbreak of disease. To summarise,

the Monograph has been revised as follows to exclude vaccines produced in rabbits from its scope, and to align it with current policy. The piglets used in the relevant tests are 6-10 weeks old (instead of 6-7 weeks old) and free from antibodies against pestiviruses (instead of swine-fever virus and bovine viral diarrhoea virus).

**Safety in piglets:** this is now a test with 10 piglets not older than the minimum age recommended for vaccination, with 10 doses of vaccine, and the body temperature is recorded; the group of piglets with administration of prednisolone has been deleted.

**Safety in pregnant sows:** primiparous sows have been replaced by sows or gilts and the test is now carried out with only 1 dose of vaccine instead of 2; administration of sodium chloride in the controls has been deleted; the body temperature is recorded and piglets born are controlled.

**Non-transmissibility:** the challenge has been deleted and alternative methods are used to detect classical swine-fever virus in the controls.

**Increase in virulence:** the passage requirement has been lowered to 5 (like in other monographs); the quantity

of blood administered has been lowered to 2 ml; blood samples are collected daily between days 2 and 7 post-vaccination.

**Immunogenicity:** the PD<sub>50</sub> test has been changed.

**Identification:** test A has been deleted since it was used to identify the vaccine produced in rabbits.

**Extraneous agents:** the test in mice has been deleted since it does not provide extra information.

**Safety:** 2 healthy piglets are used instead of 3, and the observation period is now 14 days instead of 21; the phrase 'in apparent good health' has been clarified.

**Virus titre:** a titration of the vaccine virus for vaccines prepared in cell cultures has been added.

**Vibriosis (cold-water) vaccine (inactivated) for salmonids (1580)**

**Vibriosis vaccine (inactivated) for salmonids (1581)**

Since additional experience has been gained with fish vaccines in the last few years, the development safety studies are performed on 1 batch of vaccine instead of 3. For other veterinary vaccines, development safety studies are always required only on 1 batch of vaccine. Furthermore, this proposal is in line with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes.

## RADIOPHARMACEUTICAL PREPARATIONS

**Chromium (<sup>51</sup>Cr) Edetate injection (0266)**

**Radiochemical purity:** zone electrophoresis replaced by a test applying paper chromatography, since the high-voltage electrophoresis equipment described is no longer available on the market.

**Fludeoxyglucose (<sup>18</sup>F) Injection (1325)**

**Radiochemical synthesis:** in view of the fact that 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose nowadays is prepared almost exclusively by a nucleophilic substitution reaction with [<sup>18</sup>F]fluoride on tetraacetylmannose triflate, the monograph now applies only to 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose prepared by nucleophilic substitution.

For this reason, the definition and the paragraph on radiochemical synthesis have been modified.

**Starting materials:** the paragraph on starting materials has been deleted due to the elaboration of separate monographs on these materials.

**2-Fluoro-2-deoxy-D-glucose and impurity A:** the limit for 2-fluoro-2-deoxy-D-glucose has been decreased to 0.5 mg/V.

**Impurity B:** TLC test for aminopolyether has been replaced by a more efficient and practical spot test.

**Radionuclidic purity:** the limit for the radioactivity due to fluorine-18 has been tightened from 99.0 per cent to 99.9 per cent; more details are given on the analytical procedure.

## MONOGRAPHS

**Acacia (0307)**

**Functionality-related characteristics:** this section has been added since acacia is used as suspending agent and viscosity-increasing agent; apparent viscosity is therefore indicated.

**Acacia, spray-dried (0308)**

**Functionality-related characteristics:** the section has been added since spray-dried acacia is used as suspending agent and/or viscosity increasing agent; apparent viscosity is therefore indicated.

**Aceclofenac (1281)**

**Related substances:** the CRS for quantification of impurity I (*diclofenac impurity A CRS*) is now produced by evaporation; accordingly, reference solution (d) has been modified and reference solution (f) has been added; in line with current policy, the 2 last gradient steps, corresponding to column equilibration, have been deleted as column equilibration is considered to be standard analytical practice.

**Alginic acid (0591)**

**Functionality-related characteristics:** alginic acid is used as disintegrant and/or binder, and as gelling agent or viscosity-increasing agent; for the 1<sup>st</sup> set of characteristics, particle-size distribution and settling volume have been retained; for the 2<sup>nd</sup> set, apparent viscosity has been introduced.

**Birch leaf (1174)**

**Identification B:** illustration of the powdered drug added.

**Calcium Carbonate (0014)**

**Functionality-related characteristics:** calcium carbonate is mainly used as filler in capsules and tablets, and characteristics common to other fillers have therefore been retained.

**Calcium dobesilate Monohydrate (1183)**

**Definition:** upper limit of content decreased to 101.0 based on batch data and in accordance with current policy.

**Related substances:** TLC test for hydroquinone replaced by LC test for related substances in accordance with current policy.

**Capsicum (1859)**

**Identification B:** illustration of the powdered drug added.

**Cellulose, microcrystalline (0316)**

**Functionality-related characteristics:** degree of polymerisation and crystallinity have been deleted because scientific literature has shown no effect of these characteristics on the function of microcrystalline cellulose as binder, diluent or disintegrant; there is, however, literature showing effects of crystallinity on water sorption properties, which may impact the chemical stability of the final preparation.

**Cellulose, powdered (0315)**

**Functionality-related characteristics:** degree of polymerisation and crystallinity have been deleted because scientific literature has shown no effect of these characteristics on the function of powdered cellulose as diluent or disintegrant.

**Cinchona bark (0174)**

**Identification B:** illustration of the powdered drug added; description of the phloem parenchyma added since this has been observed by microscopy.

**Cyclizine hydrochloride (1092)**

**Identification B:** the indication to use discs for sample preparation has been deleted to allow other methods of preparation that are increasingly used.

**Identification C:** TLC test formerly used for both identification and related substances test revised and now described under Identification.

**Related substances:** TLC replaced by GC.

**Impurities:** introduction of additional impurity covered by GC.

**Devil's claw root (1095)**

**Identification B:** illustration of the powdered drug added.

**Dihydrostreptomycin sulphate for veterinary use (0485)**

**Related substances:** introduction of an improved system suitability test.

**Etamsylate (1204)**

**Identification B:** for IR, the specification to use discs has been deleted since other methods of sample preparation are also acceptable.

**Related substances:** TLC for hydroquinone replaced by LC for related substances in accordance with current policy.

**Impurities:** impurity A specified.

**Ginger (1522)**

**Identification B:** illustration of the powdered drug added.

**Glucose, liquid (1330)**

**Loss on drying:** the operating conditions have been changed from 'reduced pressure' to 'high vacuum' in accordance with the general method.

**Human anti-D immunoglobulin (0557)**

**Definition:** it is clearly stated that the test for anti-D antibodies (2.6.26) that is required in the monograph *Human normal immunoglobulin (0338)* does not have to be carried out, since an assay of human anti-D immunoglobulin (2.7.13) is prescribed under Potency.

**Human normal immunoglobulin (0338)**

**CAS number:** it has been deleted.

**Definition and Production:** since subcutaneous administration of human normal immunoglobulin is being employed to an increasing extent as an alternative to intravenous immunoglobulin in the treatment of primary immunoglobulin deficiencies, this route has been added together with a requirement to test for Fc function if it is intended for this use; both the capacity to bind appropriate antigens and to mediate Fc-dependent functions have to be demonstrated to prove functional integrity of the antibodies in the preparations, since both capacities are necessary conditions of a satisfactory therapeutic efficacy.

**Tests:** 2 additional tests have to be performed when human normal immunoglobulin is intended for subcutaneous administration: a test for anti-A and anti-B haemagglutinins (2.6.20) and a test for anti-D antibodies (2.6.26); this is in line with EMEA guidelines.

**Human plasma for fractionation (0853)**

**Laboratory tests:** since there is good agreement in the scientific community that the test for alanine aminotransferase (ALT) is no longer needed (see position paper on ALT testing CPMP/BWP/385/99), and since a lot of European countries delete this test from their national requirements, the reference to this test is deleted.

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

**Production:** the requirement for testing for hepatitis C virus antibodies in the plasma pool has been deleted as this has already been done for human plasma for fractionation.

**Assay:** it is required that the production process guarantees the integrity of coagulation proteins; indeed, certain inactivation methods reduce the levels of some of these proteins, sometimes significantly, which may result in severe complications for some patients: limits for human protein C and human plasmin inhibitor ( $\alpha$ -2-antiplasmin) are indicated, whereas human protein S is within the limits approved for the particular product. Regarding Factor V, a reference to the International Standard has been added and the volumes given in the assay description have been replaced by volume ratios. A reference to the International Standard has also been added for factor XI.

**Thromboplastin R:** the description of this reagent has been updated.

**Hydroxypropylbetadex (1804)**

**Related substances:** to take account of the fact that the return to the stable baseline could take rather long, the run time in the test has been changed from 3 times to 6 times the retention time of impurity A.

**Imipramine hydrochloride (0029)**

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

**Heavy metals:** test modified in accordance with current policy.

**Magnesium carbonate, heavy (0043)**

**Identification A:** due to the adoption of chapter 2.9.34, and therefore the deletion of chapter 2.9.15, the specification has been adapted.

**Functionality-related characteristics:** heavy magnesium carbonate is mainly used as filler for direct compression; characteristics common to other fillers have therefore been retained.

**Methyltestosterone (0410)**

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

**Metoclopramide (1348)**

**Identification B:** specification to use discs for sample preparation deleted to allow other methods that are increasingly used.

**Related substances:** relative retentions of specified impurities added.

**Naproxen (0731)**

**Related substances:** the LC has been harmonised with the current monograph for naproxen sodium (1702);

a number of impurities formerly dealt with as specified impurities are now covered by the limit for unspecified impurities, corresponding to batch data.

**Norfloxacin (1248)**

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

**Ofloxacin (1455)**

**Identification:** specification to use discs for sample preparation deleted to allow other methods that are increasingly used.

**Related substances:** relative retentions of specified impurities added.

**Orciprenaline sulphate (1033)**

**Characters:** solubility in ethanol (96 per cent) corrected.

**Identification B:** specification to use discs for sample preparation deleted to allow other methods.

**Related substances:** TLC replaced by LC in accordance with current policy; impurity C added as 'other detectable impurity'.

**Methanol and 2-propanol:** test deleted since it is covered by general chapter 5.4. *Residual solvents*.

**Storage:** storage in an airtight container indicated.

**Oxacillin sodium monohydrate (2260)**

**Residual solvents:** addition of a test for ethyl acetate.

**Oxfendazole for veterinary use (1458)**

**Related substances:** relative retentions of specified impurities A, B, C and D added.

**Paraffin, white soft (1799)**

**Paraffin, yellow soft (1554)**

**Characters:** solubility in methylene chloride modified to 'slightly soluble'.

**Identification B:** reference spectrum replaced by reference substance according to current policy.

**Identification C:** a light brown colour has been obtained with batches that comply with all other requirements of the monograph; it may be due to the unsaturated hydrocarbons usually present in the substance.

**Pseudoephedrine hydrochloride (1367)**

**Identification B:** specification to use discs for sample preparation deleted to allow other methods of preparation that are increasingly used.

**Related substances:** relative retention of specified impurity A added.

**Ramipril (1368)**

**Related substances:** LC method slightly modified in order to permit detection of additional impurity O, classified under 'other detectable impurities'.

**Sodium hyaluronate (1472)**

**Heavy metals:** test introduced in view of the usual dosage and routes of administration of the product.

**Assay:** now specified that reagent A must be cooled before use.

**Soya-bean oil, refined (1473)**

**Fatty acid composition:** since 2005, it appears that the fatty acid composition of some sources has changed and the stearic acid content is lower than the lower limit of the monograph, which has consequently been adapted; the oils tested are produced by refineries that exclusively produce refined soya-bean oil; the change could be attributed to climatic change, similarly to what was observed for palmitoleic acid in virgin and refined almond oils.

**Water:** the sample size, too high for the coulometric method, has been reduced in accordance with the recommendations of a supplier of the apparatus.

**St. John's wort (1438)**

**Identification A and B:** the macroscopic and the microscopic descriptions of fruits and seeds have been added. According to the definition of the monograph, the herbal drug is harvested during flowering time. As can be observed during flowering time, faded flowers occur beside flowers just opening. Therefore, fruits, partly immature, and seeds of *Hypericum perforatum* L. may be found in the herbal drug.

**Streptokinase concentrated solution (0356)**

The monograph has undergone a general revision.

**Title:** 'bulk' replaced by 'concentrated' (correct terminology, general policy).

**Identification A:** use of polystyrene tubes specified since they are the only ones that have been found suitable.

**Identification B:** details of preparation of the agar deleted to allow flexibility for the analyst; minor changes.

**Related substances:** introduction of LC test.

**Assay:** minimum number of data points reduced from 4 to 3, since in routine testing satisfactory results can be obtained with 3 dilutions; parallel-line assay is cited as an example only, to allow flexibility; confidence limits related to estimated potency in accordance with current policy.

**Sulfacetamide sodium (0107)**

**Identification D:** deleted because it prescribes an odour.

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

**Impurities:** section showing impurities controlled by introduced LC.

**Tinidazole (1051)**

**Identification C:** specification to use discs for sample preparation deleted to allow other methods that are increasingly used.

**Identification D:** TLC test formerly used for both identification and related substances now described under Identification.

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