

COMMENTS CONCERNING SOME REVISED/CORRECTED TEXTS PUBLISHED IN THE SUPPLEMENT 6.1

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

GENERAL TEXTS

2.2.60. Melting point - instrumental method

This is an additional method for introduction into the Ph. Eur. that is commonly used by industry. It may be referred to in new monographs or it may replace an existing method in monographs that are revised. Testing would need to be performed to confirm the limits.

2.9.40. Uniformity of dosage units

A number of changes are made in order to clarify the text for the users; in particular a more detailed definition of the value *T* is provided.

In addition, a modification of Mass Variation is included.

The Ph. Eur. Commission has recently accepted that monographs on preparations for cutaneous application be

supplemented with a test for uniformity of dosage units, therefore the exemption mentioned in the 1st paragraph is amended.

Finally, similarly to chapter 2.9.6. *Uniformity of content*, multivitamin and trace-element preparations are excluded from the test for content uniformity.

5.2.7. Evaluation of efficacy of veterinary vaccines and immunosera

In order to clarify interpretation of the text, this chapter has been revised to include a statement on duration of immunity, and notably to indicate that the test model described under Immunogenicity and/or Potency is not necessarily used as such to determine the claimed duration of immunity.

VACCINES FOR HUMAN USE

Measles, mumps and rubella vaccine (live) (1057)

Thermal stability test and Assay: the main changes are:

- deletion of Details regarding cell cultures and dilution steps; these details are an unnecessary restriction since the validity criteria give a better assurance of correct test design;
- limits are expressed as logarithms, in such a way that excessive rounding is avoided;
- addition of a sentence referring to the use of neutralising antisera for the assay;
- since the aim is to confirm the suitable design of the test, validity criteria apply to the reference preparation only, and on the combined value obtained from 3 replicates;
- a manufacturer's reference preparation may be used provided it is regularly compared with the appropriate BRP;
- introduction of control charts in addition to the 0.5 log CCID₅₀ criteria, in accordance with good practice;
- deletion of the requirement on the range of virus concentration found for the replicates; the requirement for closeness to the historical value for the reference preparation, together with the use of a control chart, is considered to give better control;
- Introduction of details regarding repetition of the test and combination of valid results;

- reference to chapter 5.3 for calculations;
- where justified and authorised, different assay designs may be used provided they give the same guarantee.

Labelling: the time within which the vaccine must be used after reconstitution has been deleted since it is already mentioned in the general monograph *Vaccines for human use (0153)*.

Measles vaccine (live) (0213)

Mumps vaccine (live) (0538)

Thermal stability test and Assay: the main changes are:

- Deletion of details regarding cell cultures and dilution steps; these details are an unnecessary restriction since the validity criteria give a better assurance of correct test design;
- limits are expressed as logarithms, in such a way that excessive rounding is avoided;
- since the aim is to confirm the suitable design of the test, validity criteria apply to the reference preparation only, and on the combined value obtained from 3 replicates;
- a manufacturer's reference preparation may be used provided it is regularly compared with the appropriate BRP;
- introduction of control charts in addition to the 0.5 log CCID₅₀ criteria, in accordance with good practice;

- deletion of the requirement on the range of virus concentration found for the replicates; the requirement for closeness to the historical value for the reference preparation, together with the use of a control chart, is considered to give better control;
- introduction of details regarding repetition of the test and combination of valid results;
- Reference to chapter 5.3 for calculations;
- where justified and authorised, different assay designs may be used provided they give the same guarantee.

Neurovirulence: the testing scheme has been revised to foresee the study of potential neurovirulence of the vaccine strains during preclinical development instead of performing the test for neurovirulence of live virus vaccines (2.6.18) on the seed lot; this study is based on available data, notably for wild-type virus; where necessary, a risk analysis study is considered and, where applicable, a test for neurovirulence is carried out using an animal model that differentiates wild type and attenuated virus.

Labelling: the time within which the vaccine must be used after reconstitution has been deleted since it is already mentioned in the general monograph *Vaccines for human use (0153)*.

Poliomyelitis vaccine (oral) (0215)

Thermal stability test and Assay: the main changes are:

- deletion of details regarding the method used, only the cell line remains; these details are an unnecessary restriction since the validity criteria give a better assurance of correct design;
- limits are expressed as logarithms, in such a way that excessive rounding is avoided;
- since validity criteria are described under Assay, they are not repeated for the thermal stability test;
- since the aim is to confirm the suitable design of the test, validity criteria apply to the reference preparation only, and on the combined value obtained from 3 replicates;
- a manufacturer's reference preparation may be used provided it is regularly compared with the appropriate BRP;
- introduction of control charts in addition to the 0.5 log CCID₅₀ criteria, in accordance with good practice;
- deletion of the requirement on the range of virus concentration found for the replicates; the requirement for closeness to the historical value for the reference preparation, together with the use of a control chart, is considered to give better control;
- introduction of details regarding repetition of the test and combination of valid results;
- reference to chapter 5.3 for calculations;
- where justified and authorised, different assay designs may be used provided they give the same guarantee.

Primary monkey kidney cell cultures (test in rabbits and test in guinea-pigs): some details regarding volume injections have been added for greater clarity.

Rabies vaccine for human use prepared in cell cultures (0216)

Assay: revised in order to introduce the possibility of replacing the lethal end-point by a more human end-point.

Rubella vaccine (live) (0162)

Thermal stability test and Assay: the main changes are:

- deletion of details regarding cell cultures and dilution steps; these details are an unnecessary restriction since the validity criteria give a better assurance of correct test design;
- limits are expressed as logarithms, in such a way that excessive rounding is avoided;
- since the aim is to confirm the suitable design of the test, validity criteria apply to the reference preparation only, and on the combined value obtained from 3 replicates;
- a manufacturer's reference preparation may be used provided it is regularly compared with the appropriate BRP;
- introduction of control charts in addition to the 0.5 log CCID₅₀ criteria, in accordance with good practice;
- deletion of the requirement on the range of virus concentration found for the replicates; the requirement for closeness to the historical value for the reference preparation, together with the use of a control chart, is considered to give better control;
- introduction of details regarding repetition of the test and combination of valid results;
- reference to chapter 5.3 for calculations;
- where justified and authorised, different assay designs may be used provided they give the same guarantee.

Neurovirulence: the testing scheme has been revised to foresee the study of potential neurovirulence of the vaccine strains during preclinical development instead of performing the test for neurovirulence of live virus vaccines (2.6.18) on the seed lot; this study is based on available data, notably for wild-type virus; where necessary, a risk analysis study is considered and, where applicable, a test for neurovirulence is carried out using an animal model that differentiates wild type and attenuated virus.

Labelling: the time within which the vaccine must be used after reconstitution has been deleted since it is already mentioned in the general monograph *Vaccines for human use (0153)*.

Smallpox vaccine (live) (0164)

Thermal stability test and assay: as for the other live viral vaccine monographs:

- where justified and authorised, different assay designs may be used provided they give the same guarantee;
- validity criteria have been deleted from the thermal stability test since they are already described in the assay.

The changes are mainly editorial and more practical details are given.

Varicella vaccine (live) (0648)

Assay: the main changes are:

- deletion of details regarding cell cultures and dilution steps; these details are an unnecessary restriction since the validity criteria give a better assurance of correct test design;
- limits are expressed as logarithms, in such a way that excessive rounding is avoided;
- since the aim is to confirm the suitable design of the test, validity criteria apply to the reference preparation only, and on the combined value obtained from 3 replicates;
- since the BRP is not yet available, the requirement regarding the link between the manufacturer's reference preparation and the BRP is not included in this revision;
- introduction of control charts in addition to the 0.5 log PFU criteria, in accordance with good practice;
- deletion of the requirement on the range of virus concentration found for the replicates; the requirement for closeness to the historical value for the reference preparation, together with the use of a control chart, is considered to give better control;
- introduction of details regarding repetition of the test and combination of valid results;
- reference to chapter 5.3 for calculations;
- where justified and authorised, different assay designs may be used provided they give the same guarantee.

Neurovirulence: the testing scheme has been revised to foresee the study of potential neurovirulence of the

vaccine strains during preclinical development instead of performing the test for neurovirulence of live virus vaccines (2.6.18) on the seed lot; this study is based on available data, notably for wild-type virus; where necessary, a risk analysis study is considered and, where applicable, a test for neurovirulence is carried out using an animal model that differentiates wild type and attenuated virus.

Labelling: the time within which the vaccine must be used after reconstitution has been deleted since it is already mentioned in the general monograph *Vaccines for human use (0153)*.

Yellow fever vaccine (live) (0537)

Thermal stability test and Assay: as for the other live viral vaccine monographs, the main changes are:

- limits are expressed as logarithms, in such a way that excessive rounding is avoided;
- since the aim is to confirm the suitable design of the test, validity criteria apply to the reference preparation only, and on the combined value obtained from 3 replicates;
- since there is no appropriate BRP available, the requirement regarding the link between the manufacturer's reference preparation and the BRP is not included;
- introduction of control charts in addition to the 0.5 log PFU criteria, in accordance with good practice;
- introduction of details regarding repetition of the test and combination of valid results;
- reference to chapter 5.3 for calculations;
- where justified and authorised, different assay designs may be used provided they give the same guarantee.

Test for abnormal toxicity: details regarding injection sites have been added for greater clarity.

Labelling: the period of time within which the vaccine is to be used after reconstitution has been deleted since it is already mentioned in the general monograph *Vaccines for human use (0153)*.

VACCINES FOR VETERINARY USE

Avian infectious bronchitis vaccine (live) (0442)

Safety for the respiratory tract and kidneys: the requirement for the average ciliostasis score, which should not be more than 25, has been replaced by a risk/benefit analysis of the average ciliostasis scores; indeed, since some vaccines cannot comply with the requirement of 25, but can be useful as a booster injection in a number of epidemiological situations, the test has been maintained, since it provides useful information, but without a limit.

Rabies vaccine (inactivated) for veterinary use (0451)

Potency: revised to introduce the possibility of replacing the lethal end-point by a more humane end-point.

MONOGRAPHS

Alfuzosin hydrochloride (1287)

Related substances: LC method revised to bring it in line with the current policy for the control of impurities.

Aluminium hydroxide, hydrated, for adsorption (1664)

Assay: dissolution conditions improved.

Arnica flower (1391)

Identification B: illustrations of the powdered drug added.

Atropine (2056)

Identification B: Ph. Eur. reference spectrum replaced by a CRS in accordance with current policy.

Related substances: the column used in the test is no longer available at a suitable quality, so a new method that shows better specificity and improved peak symmetry has been developed.

Atropine sulphate (0068)

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

Bearberry leaf (1054)

Assay: arbutin CRS introduced; reference solution (b) added for system suitability.

Butcher's broom (1847)

Identification B: illustration of the powdered drug added.

Caffeine (0267)

Related substances: TLC replaced by LC.

Carbomers (1299)

Identification A: the IR absorption bands observed with the products on the market have been added; the bands listed are flexible enough to account for any variability in accuracy and precision in the methodology and instrumentation.

Cefadroxil monohydrate (0813)

Absorbance test at 330 nm: this test has been deleted, since the impurities concerned are controlled by the related substances test.

Absorbance at 264 nm: this test, which is in fact partly an identification test and a potency determination, has been deleted, since both aspects are covered by other tests in the monograph.

Cefalexin monohydrate (0708)

Absorbance test at 330 nm: this test has been deleted, since the impurities concerned are controlled by the related substances test.

Absorbance at 262 nm: this test, which in fact is partly an identification test and a potency determination, has been deleted, since both aspects are covered by other tests in the monograph.

Chlorphenamine maleate (0386)

Related substances: modification of reference solution (d) and addition of reference solution (e).

Clotrimazole (0757)

Identification: a TLC test is now described under this section and test D has been deleted.

Appearance of solution: the test has been deleted since the substance is not used in parenteral preparations.

Related substances: an LC test has been introduced to replace the TLCs previously described in the (2-chlorophenyl)diphenylmethanol and imidazole tests, in accordance with the current policy.

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

Codeine (0076)

Identification C: Ph. Eur. reference spectrum replaced by a CRS in accordance with current policy.

Devil's claw root (1095)

Assay: method harmonised with that of the monograph *Devil's claw dry extract (1871)*.

Identification B: minor changes to the description of the powdered drug.

Identification C: fructose added to the reference solution.

Diethyl phthalate (0897)

Water: sample size increased to give sufficient accuracy in titration.

Dihydroergotamine mesilate (0551)

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

Diltiazem hydrochloride (1004)

Related substances: reference solutions (a) and (b) have been revised as diltiazem impurity A is now produced by evaporation.

Disodium phosphate dodecahydrate (0118)

Water: *formamide R1* is prescribed instead of *formamide R* as a component of the solvent.

Assay: a small mistake in the calculation of the water content (for example 0.1 per cent) has serious repercussions on the calculations in the assay (0.25 per cent in this case); therefore, the limits of content of the substance are given as is, without allowing for the results of the test for water.

Doxepin hydrochloride (1096)

Identification C: Ph. Eur. reference spectrum replaced by a CRS in accordance with current policy.

Related substances: TLC replaced by LC.

Estradiol benzoate (0139)

Related substances: test updated in light of current batch data; new specified impurity G and other detectable impurity H added; correction factor for impurity A introduced.

Ethambutol hydrochloride (0553)

Identification: only the 1st identification series has been kept as the substance is not used in pharmacies.

1,2-Dichloroethane: this test has been introduced.

Related substances: an LC method has been introduced to improve the control of impurities.

Assay: the assay by optical rotation has been replaced by a titration method.

Glutathione (1670)

Related substances: limit for impurity C increased to 1.5 per cent, based on batch data.

Goldenseal rhizome (1831)**Hamamelis leaf (0909)**

Identification B: illustration of the powdered drug added.

Hop strobile (1222)

Identification B: illustration of the powdered drug added; description of glandular trichomes added since these were observed by microscopy.

Hypromellose phthalate (0347)

Assay: determination of phthaloyl groups has been moved to functionality-related characteristics, since the phthaloyl content is used to define grades with distinct functionalities.

Solubility: it has been added that the substance does not dissolve in 0.1 M hydrochloric acid, since this is the basis of its function as a gastro-resistant coating agent.

Ibuprofen (0721)

Related substances: the list of specified impurities has been revised and the limits have been tightened in view of the high purity of the batches on the market; given the MAXimum daily dose of > 2 g/day the limits for unspecified impurities have been adapted to the requirements of the general monograph *Substances for pharmaceutical use (2034)*; a CRS for peak identification of the specified impurities has been added.

Lidocaine (0727)

Identification: the verification of the melting point in addition to the IR is unnecessary and has been deleted from the 1st series; the 2nd series has been simplified to avoid the use of toxic reagents.

Appearance of solution, Heavy metals: these tests have been deleted because the substance is not intended for parenteral use.

Related substances: the TLC for impurity A has been replaced by an LC, which allows the control of impurity A and other related substances.

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

Liothyronine sodium (0728)

Appearance of solution: deleted.

Specific optical rotation: solution S now described in this test.

Related substances, Assay: replacement of the CL method.

Impurities: addition of the section.

Lymecycline (1654)

Light-absorbing impurities: concentration of the test solution increased in order to make the test pertinent and to bring it in line with those described in monographs of the same family of substances.

Related substances: relative retention of impurity A corrected; the value is based upon results from an interlaboratory study.

Morphine hydrochloride (0097)**Morphine sulphate (1244)**

Related substances: LC changed to obtain better separation of impurities; impurity E indicated as specified.

Nifuroxazide (1999)

Identification: Ph. Eur. reference spectrum replaced by a CRS in accordance with current policy.

Related substances: LC method replaced by one that controls an additional impurity present in the batches but not separated from the principal peak with the previous method.

Povidone (0685)

Within the framework of international harmonisation, the following tests have been modified.

Identification: identification E has been revised.

Viscosity, expressed as K-value, Aldehydes, Peroxides, Hydrazine, Impurity A: several minor changes have been made.

Formic acid: this test has been added, as there is no test for loss on drying and the water content can be up to 5 per cent.

Impurity B: the column, the detection, the injection and the system suitability have been revised.

Assay: changes in the wording have been made.

Roselle (1623)

Identification C: in order to validate the separation and spacing between the zones, a 2nd reference substance has been added to the TLC reference solution.

Spiramycin (0293)

Related substances: improvement of *in-situ* degradation procedure to obtain impurity A.

Impurities: C is no longer listed as specified but as other detectable.

Sultamicillin (2211)

Assay: correction factor added for the calculation of content.

Water: precision of the mass of the substance to be examined modified.

Storage: the substance can be stored at room temperature, so the storage temperature has been deleted.

Tetracaine hydrochloride (0057)

Related substances: TLC replaced by LC.

Storage: use of an airtight container has been added since the substance is hygroscopic.

Triamterene (0058)

Identification: IR absorption spectrophotometry allows a suitable specific identification of the substance and has been introduced in replacement of UV spectrophotometry and fluorescence.

Related substances: the TLCs for impurity A and related substances have been replaced by LC in accordance with

current policy; a GC has also been introduced to control impurity D.

Impurities: section introduced showing impurities controlled by the LC and GC tests.

Triglycerol diisostearate (2032)

Sulphated ash: limit raised to 0.5 per cent; sodium from the catalyst may be present.

Willow bark (1583)

Assay: harmonised with the monograph *Willow bark dry extract (2312)*.

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ISBN 978-92-871-6037-9

Price: 15 EUR (Europe) / US\$ 23 (outside Europe), + 10 % postage.

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