

## COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN SUPPLEMENT 4.6

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the November 2002 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

#### 2.2.46. Chromatographic separation techniques

Corrections have been published by mistake in Supplement 4.5. The text to be taken into account is the version published in the main volume of the 4<sup>th</sup> Edition, that is republished in Supplement 4.6.

#### 2.4.13. Sulphates

The method has been revised to increase the volume prepared to enable the required volume (2.5 ml) to be sampled. The conditions of the test are not changed in any way.

#### 2.6.1. Sterility

The text has been revised within the framework of international harmonisation with the USP and the JP.

#### 2.7.20. *In vivo* assay of poliomyelitis vaccine (inactivated)

This chapter has been revised to clarify specification of sex and weight homogeneity of the animals used in the test on rats:

- addition of an equal distribution of males and females between groups,
- addition of a specification related to the weight of all animals as specified in the collaborative

study for the establishment of a rat bioassay for inactivated poliomyelitis vaccine (Pharmeuropa BIO 2000-1),

- suppression of the specification related to weight of individual animals with regard to the group.

#### 2.9.1. Disintegration of tablets and capsules

A statement on the type of apparatus to be used depending on the size of the dosage form has been proposed, which corresponds to the statement of the USP.

- Apparatus A: the method is currently being examined within the scope of International Harmonisation. It was agreed not to change the specification for dimensions of the apparatus until the harmonisation process is completed. Therefore only minor changes have been introduced.

- Apparatus B: this apparatus is not on the list of topics to be harmonised at the present time. Based on data received from manufacturers, some dimensions have been modified. The methodology has been reviewed since an error was introduced when the chapter was elaborated (test to be performed on 6 dosage units instead of 3 units).

### GENERAL TEXTS

#### 5.4. Residual solvents

This chapter has been revised in order to:

- align the introductory paragraphs with the present practice and policy of the Commission;

- specify the calculation of assay content for a substance containing a residual solvent;
- incorporate new classification and/or limits for the 2 solvents *N*-methylpyrrolidone and tetrahydrofuran recently dealt with by the ICH Residual Solvents Maintenance Group.

### GENERAL MONOGRAPHS

#### Substances for pharmaceutical use (2034)

The related substances section has been revised in order to align it with the revised ICH Guideline [Q3A(R)] on impurities in drug substances. The calculation of assay content for a substance containing a residual solvent has been revised in the Residual solvents section.

#### Vaccines for veterinary use (0062)

This general monograph has been revised to be applicable to all veterinary vaccines, including vaccines for which there is not a specific monograph. The following notable features are:

- addition of a Potency and Immunogenicity section, which clarifies the purpose of these two parts of the monographs;
- addition of sections on Route of administration, Methods of administration, and Categories of animals. Some monograph requirements are linked to the route of administration and this series of definitions is therefore needed;
- addition of a section on humane end-points (Animal tests);
- the section on batch safety testing has been expanded, notably to cover evaluation of the test, the possibility of waiving the test for established vaccines, and the immune status of the animals to be used.

## DOSAGE FORMS

### Parenteral preparations (0520)

In the bacterial endotoxins test the temporary exemption for preparations presented in volumes

below 15 ml has been deleted, in accordance with the decisions taken by the Commission during its November 2000 session. However the exemption has been kept for preparations for veterinary use.

## MONOGRAPHS

### Acacia (0307)

Acacia seyal Del. has been added to the botanical definition. As a result of this, the identification based on optical rotation has been deleted.

### Acacia, spray-dried (0308)

Acacia seyal Del. has been added to the botanical definition of Acacia. As a result of this, the identification based on optical rotation has been deleted. Identification A has been harmonised with that of Acacia (traces of starch granules may be present).

### Chlorothiazide (0385)

In the assay, 0.1 M tetrabutylammonium hydroxide, which requires toluene (a class 2 solvent) for its preparation, has been replaced by 0.1 M tetrabutylammonium hydroxide in 2-propanol, which uses 2-propanol (a class 3 solvent) instead.

### Ciprofloxacin (1089)

To take into account the improvement of the quality of this substance, changes have been introduced to the test for appearance of solution, and to the limits for any other impurity in the test for related substances.

### Ciprofloxacin hydrochloride (0888)

To take into account the improvement of the quality of this substance, changes have been made to the test for appearance of solution, the test for pH and the limits for any other impurity in the test for related substances.

### Citric acid, anhydrous (0455)

### Citric acid monohydrate (0456)

Changes have been made to these monographs within the framework of international harmonisation with the USP and the JP.

### Colistin sulphate (0320)

The method for microbiological titration has been replaced by an LC method that separates more than 10 components of colistin sulphate.

### Fluocinolone acetonide (0494)

The preparation of reference solution (a) has been revised to improve resolution and to fulfill the system suitability requirement with most of the usual columns.

### Gentian root (0392)

The TLC identification test has been revised in order to harmonise the monograph with that of the tincture and to replace the chloroform used in the mobile phase.

### Gentian tincture (1870)

The TLC identification test has been revised in order to harmonise the monograph with that of the drug and to replace the methylene chloride used in the mobile phase.

### Gramicidin (0907)

The test for absorbance has been replaced by a test for composition by LC. The structures of the main compounds defining gramicidin and of the impurities separated by this LC method have been added.

### Heparin calcium (0332)

### Heparin sodium (0333)

The use of freshly shed blood for an identification test is impractical. Recalcified, citrated sheep plasma, as used in the assay can serve the same purpose.

### Human albumin solution (0255)

Following the report of an EDQM proficiency testing study, some improvements have been made to the description of the test for molecular-size distribution.

### Human anti-D immunoglobulin (0557)

### Human anti-D immunoglobulin for intravenous administration (1527)

The monographs have notably been revised to introduce requirements concerning immunisation of donors, and to introduce testing of the plasma pool for B19 virus, since the product is used in a vulnerable group of patients.

### Hydrochlorothiazide (0394)

In the assay, 0.1 M tetrabutylammonium hydroxide, which requires toluene (a class 2 solvent) for its preparation, has been replaced by 0.1 M tetrabutylammonium hydroxide in 2-propanol, which uses 2-propanol (a class 3 solvent) instead.

### Ipecacuanha liquid extract, standardised (1875)

### Ipecacuanha tincture, standardised (1530)

In the assay, anhydrous aluminium oxide has been replaced by basic aluminium oxide and a blank titration has been introduced. Basic aluminium oxide permits the release of all alkaloids of ipecacuanha but also of other undesirable alkaline substances, of which the quantity has to be determined by a blank titration.

### Ipratropium bromide (0919)

The TLC is described under Tests as it covers impurity A of saponification, which is not visible by LC. The TLC is also used for identification purposes. The LC has

been revised to cover the test for apo-ipratropium which has therefore been deleted, consequently, the list of impurities has been modified.

#### **Lactitol monohydrate (1337)**

A modification of the LC method used in the test for related substances and the assay has been made to delete the normalisation procedure and change the limits of content and impurities.

#### **Lactose, anhydrous (1061) Lactose monohydrate (0187)**

These monographs have been revised within the framework of international harmonisation with the USP and the JP.

#### **Loperamide hydrochloride (0929)**

The monograph has been revised to harmonise with the monograph on loperamide oxide monohydrate (1729). Polymorphism is indicated under Characters with deletion of the melting point information. IR is sufficient for identification purposes: a recrystallisation step is introduced for polymorphism. The test for appearance of solution has been deleted as the compound is not marketed as an injectable. The LC has been adapted to the same extent as for loperamide oxide monohydrate. A system suitability CRS has been introduced because a correction factor is applied for impurities A and D. Based on the results of recent production batches, the limits for impurities have been narrowed for individual impurities and for the total.

#### **Minocycline hydrochloride (1030)**

The TLC method used in identification A has been revised. The same TLC method is proposed for the identification of the other cyclines, with the exception of the substances used for system suitability which change depending on the cycline considered.

#### **Nystatin (0517)**

The structure of the main compound, nystatin A1, has been indicated. Under Identification, the current tests are now in the second identification series and IR and LC constitute the first identification series.

#### **Papaverine hydrochloride (0102)**

The TLC in the test for related substances has been replaced by an LC which covers both synthetic and natural papaverine.

#### **Peppermint oil (0405)**

A test for isopulegol has been introduced which allows differentiation of *Mentha piperita* (maximum 0.2 per cent of isopulegol) from *Mentha arvensis* (1 to 3 per cent of isopulegol). Furthermore, the parameters used in the chromatographic profile have been harmonised with the monograph on Mint oil, partly dementholised (1838).

#### **Polysorbate 20 (0426)**

#### **Polysorbate 60 (0427)**

#### **Polysorbate 80 (0428)**

The monographs have been revised in their entirety to harmonise with other monographs for ethoxylate derivatives.

#### **Sodium chloride (0193)**

Changes have been made to the monograph within the framework of international harmonisation with the JP and the USP.

#### **Streptokinase bulk solution (0356)**

The monograph has been revised in its entirety, following the recommendations of a Working Party involving European Experts and streptokinase manufacturers. The name of the monograph was changed to Streptokinase bulk solution, since the monograph refers to bulk streptokinase, which is a solution, and not to the final product, which is a lyophilisate. The specific activity was increased to 96 000 IU/mg, which more appropriately reflects the quality of streptokinase preparations. The composition of the imidazole buffer pH 6.5 used in the test for Streptodornase was modified according to the recommendations from a manufacturer. The assay was revised in order to avoid the use of bovine euglobulins and replace them with a more readily available reagent (chromogenic substrate). The performance of the new assay method was recently verified in the collaborative study organised by NIBSC, for the establishment of the 3<sup>rd</sup> International Standard for Streptokinase.

## **VACCINES FOR VETERINARY USE**

#### **Anthrax spore vaccine (live) for veterinary use (0441)**

Together with the revision of the general monograph on Veterinary vaccines (0062), this monograph has been revised to include immune status 1 of animals used in the safety test. They must be free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine.

#### **Bovine parainfluenza virus vaccine (live), freeze-dried (1176)**

Together with the revision of the general monograph on Vaccines for veterinary use (0062), this monograph has been revised to include immune status 2 of animals used in the safety test: they are preferably

free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine, but animals with a low level of such antibodies may be used as long as they have not been vaccinated and the administration of the vaccine does not cause an anamnestic response.

#### **Brucellosis vaccine (live) (*Brucella melitensis* Rev. 1 strain), freeze-dried, for veterinary use (0793)**

Together with the revision of the general monograph on Veterinary vaccines (0062), this monograph has been revised to include immune status 1 of animals used in the safety test: they must be free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine.

**Canine adenovirus vaccine (inactivated) (1298)**  
**Canine parvovirus vaccine (inactivated) (0795)**

Together with the revision of the general monograph on Vaccines for veterinary use (0062), these monographs have been revised to include immune status 2 of animals used in the safety test: they are preferably free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine, but animals with a low level of such antibodies may be used as long as they have not been vaccinated and the administration of the vaccine does not cause an anamnestic response.

**Canine parvovirus vaccine (live) (0964)**

Together with the revision of the general monograph on Veterinary vaccines (0062), this monograph has been revised to include immune status 1 of animals used in the safety test: they must be free from antibodies against the virus/bacterium toxin etc. contained in the vaccine.

**Clostridium botulinum vaccine for veterinary use (0360)**

**Clostridium chauvoei vaccine for veterinary use (0361)**

**Clostridium novyi (type B) vaccine for veterinary use (0362)**

**Clostridium perfringens vaccine for veterinary use (0363)**

**Clostridium septicum vaccine for veterinary use (0364)**

Together with the revision of the general monograph on Veterinary vaccines (0062), these monographs have been revised to include immune status 3 of animals used in the safety test: they must not have been vaccinated against the disease the vaccine is intended to prevent.

**Egg drop syndrome '76 vaccine (inactivated) (1202)**

Duck hepatitis virus 2 is no longer found as an infective agent of poultry and its inclusion in the list of extraneous agents to be tested for is no longer necessary and can be impractical if live virus has to be used for the test, for example by serum neutralisation.

**Equine influenza vaccine (inactivated) (0249)**

Together with the revision of the general monograph on Vaccines for veterinary use (0062), this monograph has been revised to include immune status 2 of animals used in the safety test: they are preferably free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine, but animals with a low level of such antibodies may be used as long as they have not been vaccinated and the administration of the vaccine does not cause an anamnestic response.

**Feline calicivirus vaccine (inactivated) (1101)**

Together with the revision of the general monograph on Vaccines for veterinary use (0062), this monograph

has been revised to include immune status 2 of animals used in the safety test: they are preferably free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine, but animals with a low level of such antibodies may be used as long as they have not been vaccinated and the administration of the vaccine does not cause an anamnestic response.

**Feline calicivirus vaccine (live), freeze-dried (1102)**

Together with the revision of monographs on Veterinary vaccines, this monograph has been revised to replace "susceptible animals" by immune status 1 animals in the safety test: they must be free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine.

**Feline infectious enteritis (feline panleucopenia) vaccine (inactivated) (0794)**

Together with the revision of the general monograph on Vaccines for veterinary use (0062), this monograph has been revised to include immune status 2 of animals used in the safety test: they are preferably free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine, but animals with a low level of such antibodies may be used as long as they have not been vaccinated and the administration of the vaccine does not cause an anamnestic response.

**Feline infectious enteritis (feline panleucopenia) vaccine (live) (0251)**

Together with the revision of monographs on Veterinary vaccines, this monograph has been revised to add the reference to "canine parvovirus" as in the inactivated vaccine (0794).

**Feline viral rhinotracheitis vaccine (inactivated) (1207)**

Together with the revision of the general monograph on Vaccines for veterinary use (0062), this monograph has been revised to include immune status 2 of animals used in the safety test: they are preferably free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine, but animals with a low level of such antibodies may be used as long as they have not been vaccinated and the administration of the vaccine does not cause an anamnestic response.

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

Together with the revision of the general monograph on Vaccines for veterinary use (0062), this monograph has been revised to include immune status 2 of animals used in the safety test: they are preferably free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine, but animals with a low level of such antibodies may be used as long as they have not been vaccinated and the administration of the vaccine does not cause an anamnestic response.

**Infectious bovine rhinotracheitis vaccine (live), freeze-dried (0696)**

Together with the revision of monographs on Veterinary vaccines, this monograph has been revised to replace "susceptible animals" by immune status 1 animals in the reversion to virulence and the safety tests: they must be free from antibodies against the virus/bacterium toxin etc. contained in the vaccine.

**Neonatal piglet colibacillosis vaccine (inactivated) (0962)**

In the development safety section, the standard tests applied to other vaccines for pigs have been included because the previous tests were described in less detail and were subject to divergent interpretation.

In colibacillosis vaccines, the levels of bacterial endotoxins are very high and are probably the most important factor in adverse reactions. With such high levels, the value found for a batch depends on the method used so that an acceptable limit applicable to all vaccines cannot be given. It has been decided to link the limit to the level of endotoxin found in batches that were subjected to safety testing and found satisfactory. While this will ensure safety, it may be too strict if the batches tested during development happened to have a relatively low level of bacterial endotoxins, particularly when the large variance of the method is taken into account. The possibility of redefining the limit in the light of subsequent testing of production batches is therefore provided for.

The batch safety test has been modified to delete requirement for a second injection and to add a requirement for measurement of body temperature following administration of the vaccine. A second dose of vaccine is unlikely to yield useful information with a test using only 2 animals. Measurement of body temperature gives an objective measure of reaction to the vaccine. The immune status of animals has also been modified according to current policy.

For the potency test, difficulties were encountered with the acceptance criteria the reason for which has not been well established. The revised test includes a scale for scoring clinical signs and for strains with which it is difficult to produce severe clinical signs in experimental conditions a modified validity criteria are proposed.

**Neonatal ruminant colibacillosis vaccine (inactivated) (0961)**

In the development safety test, a requirement for measurement of body temperature after administration of the vaccine has been introduced. This change is in relation with the modifications to the limit for bacterial endotoxins.

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method used so that an acceptable limit applicable to all vaccines cannot be given. It has been decided to link the limit to the level of endotoxin found in batches that were subjected to safety testing and found satisfactory. While this will ensure safety, it may be too strict if the batches tested during development happened to have a relatively low level of bacterial endotoxins, particularly when the large variance of the method is taken into account. The possibility of redefining the limit in the light of subsequent testing of production batches is therefore provided for.

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The potency test has been modified as a result of reports of difficulties in interpreting the requirements and also to allow a more convenient test model whereby colostrum from vaccinated dams may be fed to calves other than their offspring. A scale for scoring clinical signs has been added which takes account of diarrhoea rather than general signs of disease.

**Porcine actinobacillosis vaccine (inactivated) (1360)**

In actinobacillosis vaccines, the levels of bacterial endotoxins are very high and are probably the most important factor in adverse reactions. With such high levels, the value found for a batch depends on the method used so that an acceptable limit applicable to all vaccines cannot be given. It has been decided to link the limit to the level of endotoxin found in batches that were subjected to safety testing and found satisfactory. While this will ensure safety, it may be too strict if the batches tested during development happened to have a relatively low level of bacterial endotoxins, particularly when the large variance of the method is taken into account. The possibility of redefining the limit in the light of subsequent testing of production batches is therefore provided for.

**Porcine progressive atrophic rhinitis vaccine (inactivated) (1361)**

In the development safety section, the standard tests applied to other vaccines for pigs have been included because the previous tests were described in less detail and were subject to divergent interpretation. In this vaccine, the level of bacterial endotoxins is very high and is probably the most important factor in adverse reactions. With such high levels, the value found for a batch depends on the method used so that an acceptable limit applicable to all vaccines cannot be given. It has been decided to link the limit to the level of endotoxin found in batches that were subjected to safety testing and found satisfactory. While this will ensure safety, it may be too strict if the batches tested during development happened to have a relatively low

level of bacterial endotoxins, particularly when the large variance of the method is taken into account. The possibility of redefining the limit in the light of subsequent testing of production batches is therefore provided for. The batch safety test has been modified to delete the requirement for a second injection since this is unlikely to yield useful information in a test with only 2 animals.

**Rabies vaccine (inactivated) for veterinary use (0451)**

Together with the revision of monographs on Veterinary vaccines, this monograph has been revised to replace “seronegative animals” by immune status 1 animals in the safety test: they must be free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine.

**Swine erysipelas vaccine (inactivated) (0064)**

This monograph presents a new batch potency test using a serological model rather than virulent

challenge. The test has been evaluated in the Biological Standardisation Programme of EDQM and a reference coating antigen has been developed to facilitate introduction of the test, which has clear advantages from the point of view of animal welfare. The immune status of animals used in the safety test has been modified according to current policy. In the potency test, the requirement for typical signs has been set at 80 per cent rather than 90 per cent. This change is not considered to modify the requirement significantly but allows for variation in the test animals.

**Tetanus vaccine for veterinary use (0697)**

Together with the revision of monographs on Veterinary vaccines, this monograph has been revised to replace “susceptible animals” by immune status 1 animals in the safety test under the Production section: they must be free from antibodies against the virus/bacterium/toxin etc. contained in the vaccine.

## SUTURES FOR HUMAN USE

**Sutures, sterile non-absorbable (0324)**

The monograph has been revised to extend the scope to cover poly(vinylidene difluoride) (PVDF) and stainless steel sutures.