

## Comments concerning revised texts published in the 9<sup>th</sup> Edition (9.0)

*The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November 2015 session and published in the 9<sup>th</sup> Edition (9.0).*

*When a text has been technically revised, this is indicated by horizontal or vertical lines in the margin of 9.0. The details given below complete this information, but are not necessarily exhaustive.*

*The following details can also be consulted in the [Knowledge database](#) under View history.*

*Please also note that 753 monographs have been revised for the deletion of the test for heavy metals, they are listed [here](#).*

### GENERAL CHAPTERS

#### **2.4.24. Identification and control of residual solvents**

Introduction of 2 new class 2 solvents (tetrahydrofuran and cumene) as per the latest version of ICH Guideline Q3C(R5). Preparation of solvent solution (b) corrected to take account of low solubility in water.

#### **2.5.28. Water in gases**

Text revised to include information on the calibration of mass flow controllers for electrolytic hygrometers when using gases other than nitrogen.

#### **2.9.6. Uniformity of content of single-dose preparations**

Reference to specific dosage forms deleted since information already given in specific dosage form monographs.

#### **5.2.3. Cell substrates for the production of vaccines for human use**

With a view to harmonising with the WHO recommendations while maintaining the best testing strategies currently implemented by the manufacturers, the general chapter has been revised in depth, taking into account the corresponding WHO TRS 978 Annex 3 'Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks'.

The general revision of the text covers the following topics:

1) in the general introduction section:

- the perceived theoretical risks associated with the use of continuous cell lines (especially tumorigenic cell lines) due to the biological activity of residual cellular DNA;

- greater flexibility when testing for infectious extraneous agents between master cell bank and working cell bank, based on a risk assessment; Table 5.2.3.-1 has been updated accordingly and molecular methods are now considered;
- a definition of tumorigenicity and the concept of oncogenicity;
- a new paragraph relating to residual cellular DNA with mention of: an acceptable level based on a risk analysis (including both cell substrate and production process parameters, residual cellular DNA content and size, and selection of analytical methods); a specific level as a process performance target; the waiving of residual cellular DNA monitoring on a routine basis after validation of the process and demonstration of its consistent reduction of residual cellular DNA levels;

2) under Test methods for cell cultures:

- introduction of a test for mycobacteria as they are not detected by the sterility test and they can grow in some cells used for vaccine production;
- revision of the test for spiroplasmas where both cell and raw material origins must be taken into account;
- revision of the tests for extraneous agents in cell cultures with greater flexibility regarding the nature of the assay; merging of the 3 separate tests into one; and more-detailed detection methods;
- introduction of a different testing strategy for retroviruses depending on whether or not the cell line is known for producing retroviral particles; for cell lines producing retroviral particles, addition of an infectivity test;
- additional technical details are given for tests in animals and in eggs (only for avian cell substrates) and for *in vivo* tumorigenicity;
- introduction of a new paragraph related to the tests for specific viruses outlining the risk assessment of virus introduction due to the use of raw material of animal origin, the process of virus removal during manufacture of the product, and the selection of testing depending on the suspected contaminating viruses;
- deletion of the tests for *in vitro* tumorigenicity as tumorigenicity is an *in vivo* characteristic and the *in vitro* methods, which do not correlate perfectly with the *in vivo* assay, are considered as an optional characterisation in the general provisions.

## 5.8. Pharmacopoeial harmonisation

Additional information is presented for 5 excipient monographs and information is modified for 1 excipient monograph.

# GENERAL MONOGRAPHS

## Allergen products (1063)

The general monograph has been revised to account for the publication of separate source-material monographs for animal epithelia and outgrowths (2621), Hymenoptera venoms (2623), mites (2625), moulds (2626), and pollens (2627), which are also published in the same edition. Additional information is provided on microbial contamination of source materials.

## Vaccines for human use (0153)

**Carrier proteins:** section now included with a reference to general chapter 5.2.11. *Carrier proteins for the production of conjugated polysaccharide vaccines for human use*, published in Supplement 8.3.

## Vaccines for veterinary use (0062)

The structure of the monograph has been reorganised to present a more logical text and to facilitate the reading and understanding of the requirements applicable to all veterinary vaccines (even those having no individual monograph).

Some of the following modifications will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Production** (section 2). Further to the introduction of the consistency of production concept in the context of the 3Rs in the General Notices (Supplement 8.2), this concept has also been included in the general monograph.

**Substrates for production** (section 2-1-1). The introduction of a reference to general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, which sets upstream quality requirements for the production of inactivated vaccines that provide guarantees with regard to contamination by extraneous agents, makes the test for specified extraneous agents performed on each batch of final product obsolete. Consequently, the test for specified extraneous agents has been deleted in the related individual monographs, also published in the 9<sup>th</sup> Edition (*Newcastle disease vaccine (inactivated)* (0870); *Avian infectious bronchitis vaccine (inactivated)* (0959); *Avian infectious bursal disease vaccine (inactivated)* (0960); *Egg drop syndrome '76 vaccine (inactivated)* (1202); *Avian paramyxovirus 3 vaccine (inactivated) for turkeys* (1392); *Equine influenza vaccine (inactivated)* (0249); *Porcine influenza vaccine (inactivated)* (0963); *Feline chlamydiosis vaccine (inactivated)* (2324)).

**Media used for seed culture preparation and for production** (section 2-1-2). 'Standard formulation' is referred to in connection with consistency of production. Furthermore, in addition to the qualitative composition, the quantitative composition media used must also be recorded.

**Inactivation test.** For inactivated vaccines, the requirement for the 1<sup>st</sup> inactivation test has been moved from former section 2-1-4. Inactivation to section 2-3-1. Propagation and harvest of bacterial and viral antigens. The conditions to be fulfilled in order to omit the 2<sup>nd</sup> inactivation test have been introduced in section 3-10. Residual live virus/bacteria and/or detoxification testing. Details are given on the validation of the inactivation test and the determination of the maximum titre prior to inactivation. Consequently, this requirement has been amended in the related individual monographs, also published in the 9<sup>th</sup> Edition.

**Choice of vaccine composition and choice of vaccine strain** (section 2-2). To facilitate the reading of the general monograph, 2 subsections have been included: 2-2-1. Development studies on safety and efficacy and 2-2-1-2. Information for performing the safety and efficacy studies.

**Stability** (section 2-2-3) and **In-process stability** (section 2-5). Details on how to use stability studies, what is expected for stability with regard to intermediates and the definition of appropriate formulation and release parameters have been added.

**Formulation** (section 2-2-4). For live vaccines, information on what is expected for the virus titre or bacterial count at release has been added. Furthermore, requirements for inactivated vaccines have also been added.

**Preparation of the vaccine** (section 2-3). Consistency of production in the context of the 3Rs has been added.

**Antigen content** (section 2-4-1). This requirement, linked to consistency, has been added.

**Batch potency test** (formerly section 2-3-2). Section deleted and requirements moved mainly to section 3. Batch tests.

**Batch tests** (section 3). The paragraph related to particular circumstances is included in this section, consistency of production is explained and a non-exhaustive list of controls is given.

**Identification** (section 3-1). In the interest of animal welfare, the vaccine identification test by antibody induction in animals has been removed for all inactivated vaccines, which allows the user to identify the antigen(s) by any suitable methods, for example *nucleic acid amplification techniques* (2.6.21). This will allow manufacturers to replace animal tests with *in vitro* tests when appropriate, and reinforces the idea that it may be combined with the batch potency test (advantageous when both tests use animals). Consequently, the related individual monographs have been amended accordingly and also published in the 9<sup>th</sup> Edition.

**Bacteria and fungi** (section 3-8). This title, also used in the related individual monographs, replaces 'Sterility'.

**Extraneous agents** (section 3-9). The requirement for mammalian live vaccines has been moved from the related individual monographs to the general monograph, with 2 advantages: it is applicable to mammalian live vaccines that have no individual monograph in the European Pharmacopoeia and it is not necessary to repeat this requirement in each individual monograph.

**Residual live virus/bacteria and/or detoxification testing** (section 3-10). Conditions allowing omission of the 2<sup>nd</sup> inactivation test have been added. Consequently, the 2<sup>nd</sup> inactivation test prescribed in individual monographs (also published in the 9<sup>th</sup> Edition) may be omitted.

**Labelling** (section 5). Mention of the amount of antimicrobial preservative has been deleted from the labelling section as this information is not needed to demonstrate compliance or non-compliance with the monograph requirements.

## DOSAGE FORMS

### Powders for cutaneous application (1166)

**Labelling:** phrase 'that the preparation is for external use' deleted.

### Tampons, medicated (1155)

**Definition:** section amended.

## VACCINES FOR VETERINARY USE

### Aujeszky's disease vaccine (inactivated) for pigs (0744)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use* (0062), also published in the 9<sup>th</sup> Edition.

### Avian infectious bronchitis vaccine (inactivated) (0959)

**Substrate for virus propagation/Embryonated hens' eggs** (section 2-2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Batch tests/Specified extraneous agents** (formerly section 3-4). As general chapter 5.2.13 is now referred to in the monograph, thereby ensuring appropriate control of the starting material, the test performed on the final product has become obsolete and is therefore deleted.

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use* (0062), also published in the 9<sup>th</sup> Edition.

### Avian infectious bursal disease vaccine (inactivated) (0960)

**Substrate for virus propagation/Embryonated hens' eggs** (section 2-2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Batch tests/Specified extraneous agents** (formerly section 3-4). As general chapter 5.2.13 is now referred to in the monograph, thereby ensuring appropriate control of the starting material, the test performed on the final product has become obsolete and is therefore deleted.

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Avian paramyxovirus 3 vaccine (inactivated) for turkeys (1392)

**Substrate for virus propagation/Embryonated hens' eggs** (section 2-2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Batch tests/Specified extraneous agents** (formerly section 3-4). As general chapter 5.2.13 is now referred to in the monograph, thereby ensuring appropriate control of the starting material, the test performed on the final product has become obsolete and is therefore deleted.

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Bovine leptospirosis vaccine (inactivated) (1939)

**Batch potency test** (section 2-3-2, formerly 2-3-1). Further to the EDQM workshop 'Alternatives to the leptospirosis batch potency test', held on 26-27 January 2012, the monograph has been revised in order to introduce the possibility of using alternative methods to the method using guinea-pigs (e.g. lipopolysaccharide (LPS)-based antigen quantification), thereby contributing to animal welfare (3Rs). Manufacturers are encouraged to develop alternative *in vitro* methods to the animal test for batch release (1<sup>st</sup> option of choice) using appropriate tools such as the monitoring of production consistency and appropriate antigen quantification.

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live bacteria** (sections 2-3-1 and 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Bovine viral diarrhoea vaccine (inactivated) (1952)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Calf coronavirus diarrhoea vaccine (inactivated) (1953)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Calf rotavirus diarrhoea vaccine (inactivated) (1954)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Canine adenovirus vaccine (inactivated) (1298)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Canine leptospirosis vaccine (inactivated) (0447)

**Batch potency test** (section 2-3-2, formerly 2-3-1). Further to the EDQM workshop 'Alternatives to the leptospirosis batch potency test', held on 26-27 January 2012, the monograph has been revised so that an alternative *in vitro* method may also be used for adjuvanted vaccines. Furthermore, it was agreed by the participants of this workshop that a single, universal alternative method could not be developed due to the complexity of the vaccines. However, the workshop showed that alternative methods to the method using hamsters had already been successfully implemented in Europe, and approved by a competent authority, with a further example from the USA. These methods used lipopolysaccharide (LPS)-based antigen quantification and have been introduced in the monograph as alternative methods, thereby contributing to animal welfare (3Rs). Manufacturers are encouraged to develop alternative *in vitro* methods to the animal test for batch release (1<sup>st</sup> option of choice) using appropriate tools such as the monitoring of production consistency and appropriate antigen quantification.

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live bacteria** (sections 2-3-1 and 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Canine parvovirus vaccine (inactivated) (0795)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (sections 2-4-1 and 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

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

**Substrate for virus propagation/Embryonated hens' or ducks' eggs** (section 2-2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Batch tests/Specified extraneous agents** (formerly section 3-4). As general chapter 5.2.13 is now referred to in the monograph, thereby ensuring appropriate control of the starting material, the test performed on the final product has become obsolete and is therefore deleted.

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Equine herpesvirus vaccine (inactivated) (1613)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Equine influenza vaccine (inactivated) (0249)

**Substrate for virus propagation/Embryonated hens' eggs** (section 2-2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Feline calicivirosis vaccine (inactivated) (1101)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Feline chlamydiosis vaccine (inactivated) (2324)

**Preparation of the vaccine** (section 2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live chlamydomphila** (sections 2-3-1 and 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (sections 2-4-1 and 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Feline leukaemia vaccine (inactivated) (1321)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### **Foot-and-mouth disease (ruminants) vaccine (inactivated) (0063)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

### **Fowl cholera vaccine (inactivated) (1945)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

### **Infectious chicken anaemia vaccine (live) (2038)**

**Safety** (section 2-4-1). It is clarified in the text that the observation period of 21 days starts post-vaccination.

**Passive immunisation of chickens** (section 2-4-3-1) and **Prevention of virus excretion** (section 2-4-3-2). Both tests require solitary housing of laying hens and young chickens for a long time period, which is not the natural behaviour of hens, who normally live in small groups of 20 or less. According to Directive 2010/63/EU, Annex 3, section 3.3 'Housing', animals other than those that are naturally solitary, shall be socially housed in stable groups of compatible individuals. As it is current scientific knowledge that antibody titres in laying hens, eggs and hatched chickens are equal, it is not necessary to derive individual data for these tests. The requirements of passive immunity can therefore be tested in a group of chickens that are housed together.

### **Mannheimia vaccine (inactivated) for cattle (1944)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

### **Mannheimia vaccine (inactivated) for sheep (1946)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

### **Mycoplasma gallisepticum vaccine (inactivated) (1942)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live mycoplasmas** (sections 2-3-1 and 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

### **Newcastle disease vaccine (inactivated) (0870)**

**Substrate for virus propagation/Embryonated hens' eggs** (section 2-2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Batch tests/Specified extraneous agents** (formerly section 3-4). As general chapter 5.2.13 is now referred to in the monograph, thereby ensuring appropriate control of the starting material, the test performed on the final product has become obsolete and is therefore deleted.

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### **Pasteurella vaccine (inactivated) for sheep (2072)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

### **Porcine enzootic pneumonia vaccine (inactivated) (2448)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live mycoplasmas** (sections 2-3-1 and 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Porcine influenza vaccine (inactivated) (0963)

**Substrate for virus propagation/Embryonated hens' eggs** (section 2-2-1). Introduction of a reference to the new general chapter 5.2.13. *Healthy chicken flocks for the production of inactivated vaccines for veterinary use*, also published in the 9<sup>th</sup> Edition, which sets quality requirements that provide guarantees with regard to contamination by extraneous agents, thereby making the test for specified extraneous agents performed on the final product obsolete. This will contribute significantly to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Batch tests/Specified extraneous agents** (formerly section 3-4). As general chapter 5.2.13 is now referred to in the monograph, thereby ensuring appropriate control of the starting material, the test performed on the final product has become obsolete and is therefore deleted.

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Porcine parvovirus vaccine (inactivated) (0965)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

### Rabbit haemorrhagic disease vaccine (inactivated) (2325)

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method.

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

These modifications will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

**Residual live virus** (section 3-3). Conditions allowing omission of the second inactivation test have been added in line with the revision of the general monograph *Vaccines for veterinary use (0062)*, also published in the 9<sup>th</sup> Edition.

#### **Salmonella Enteritidis vaccine (inactivated) for chickens (1947)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

#### **Salmonella Typhimurium vaccine (inactivated) for chickens (2361)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

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

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

#### **Yersiniosis vaccine (inactivated) for salmonids (1950)**

**Identification** (section 3-1). In the interest of animal welfare, reference to the antibody induction test has been removed, thereby allowing the use of any suitable method. This will contribute to the reduction in animal use for the control of veterinary vaccines (3Rs).

## HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

#### **Aloes, Cape (0258)**

**Definition:** restricted to *Aloe ferox* Mill.

**Identification:** section revised to avoid use of disodium tetraborate (REACH) ; unspecific identification tests B and C deleted and replaced by improved TLC/HPTLC method.

**Barbados aloes:** improved TLC/HPTLC method introduced.

### Birch leaf (1174)

**Identification:** TLC replaced by HPTLC referring to general chapter 2.8.25. *High-performance thin-layer chromatography of herbal drugs and herbal drug preparations.*

### Butcher's broom (1847)

**Assay:** 'rotary evaporator' replaced by 'evaporate under reduced pressure'.

### Cascara dry extract, standardised (1844)

**Assay:** extraction solvent changed to avoid carry-over and loss of cascariosides.

### Chamomile flower, Roman (0380)

**Identification:** illustration of powdered herbal drug introduced and its legend integrated into text of Identification B; TLC in Identification C replaced by HPTLC referring to general chapter 2.8.25. *High-performance thin-layer chromatography of herbal drugs and herbal drug preparations.*

### Common selfheal fruit-spike (2439)

**Identification B:** illustration of powdered herbal drug introduced and its legend integrated into text of Identification B.

### Mastic (1876)

**Definition:** binomial name corrected to take account of current classification and to bring the monograph in line with the draft monograph of the Herbal Medicinal Products Committee.

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

**Identification:** TLC replaced by HPTLC referring to general chapter 2.8.25. *High-performance thin-layer chromatography of herbal drugs and herbal drug preparations.*

### St. John's wort dry extract, quantified (1874)

**Identification:** TLC replaced by HPTLC referring to general chapter 2.8.25. *High-performance thin-layer chromatography of herbal drugs and herbal drug preparations.*

## HOMOEOPATHIC PREPARATIONS

### Homoeopathic preparations (1038)

**Dosage forms:** reference to *Homeopathic pillules, coated (2786)* added.

### Mother tinctures for homoeopathic preparations (2029)

**2-Propanol:** it has been clarified that it is not necessary to test the mother tincture for 2-propanol when the ethanol supply chain is known, guaranteeing that the ethanol is of Ph. Eur. quality (as required by the general monograph *Homoeopathic preparations (1038)*); where there is not enough knowledge concerning the ethanol supply chain, thereby not

guaranteeing that it is of Ph. Eur. quality, a test for 2-propanol is necessary. The same approach has been taken in the monograph *Herbal drug extracts (0765)*.

**Pesticides, Heavy metals:** for both tests the limit of quantification should be verified to ensure that it is below the value to be measured.

**Aflatoxin B<sub>1</sub>:** test added giving the possibility of testing the mother tincture for aflatoxin B<sub>1</sub>; (where justified) instead of the herbal drug; as is the case for the other contaminants (pesticides and heavy metals for example), details are given on how to set limits.

### Methods of preparation of homoeopathic stocks and potentisation (2371)

**Methods 1.1.12 to 1.2.17:** new homoeopathic manufacturing methods have been introduced for aqueous macerates, aqueous digestions, aqueous decoctions, aqueous infusions, ethanolic digestions, ethanolic decoctions and ethanolic infusions; these methods have been adapted from the German Homoeopathic Pharmacopoeia (Homöopathisches Arzneibuch, HAB), and the equivalent HAB method numbers and titles are given for convenience.

**Maceration temperature:** the maximum temperature for maceration is 25 °C (Ph. Eur. definition of room temperature: 15-25 °C); any reference to a maximum temperature of 20 °C has been deleted.

**Methods 3.2.1, 3.2.2, 4.1.1:** it is now explained how higher dilutions are produced.

**New numbering and titles:** added to improve the structure of the general monograph.

**Ethanol concentrations in m/m:** deleted.

**Methods 1.1.5, 1.1.6, 1.1.7, 1.2.3, 1.2.4, 1.2.5, 1.2.9, 1.2.10, 1.2.11:** the approximate ethanol concentrations have been corrected.

### Pillules for homoeopathic preparations (2153)

**Uniformity of impregnation:** test added.

### Agaricus phalloides for homoeopathic preparations (2290)

**Assay:** new method proposed.

### Ignatia for homoeopathic preparations (2513)

**Production (method 1.1.10):** reference to a sieve deleted.

### Nux-vomica for homoeopathic preparations (2514)

**Production (method 1.1.10):** reference to a sieve deleted.

## MONOGRAPHS

### Aceclofenac (1281)

**Related substances:** disregard limit updated in line with general monograph *Substances for pharmaceutical use (2034)*.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Ammonium hydrogen carbonate (1390)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** use of the colour indicator has been replaced by a potentiometric end-point determination.

### Ampicillin (0167)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Ascorbic acid (0253)

**Impurities:** structure and nomenclature of impurities C and D corrected.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Beclometasone dipropionate (0654)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Caffeine (0267)

**Solution S:** corrected.

**Related substances:** resolution between the peaks due to impurities C and D has been modified.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Caffeine monohydrate (0268)

**Solution S:** corrected.

**Related substances:** resolution between the peaks due to impurities C and D has been modified.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Calcipotriol (2011)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Calcium acetate (2128)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Calcium hydrogen phosphate (0981)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Calcium lactate (2118)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### **Carmellose (2360)**

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

In addition, the following change has been introduced.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### **Cellulose, microcrystalline (0316)**

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

In addition, the following changes have been introduced.

**Characters:** substance slightly hygroscopic.

**Ether-soluble substances:** wording aligned with harmonised text.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**FRC:** introduction updated.

### **Cellulose, powdered (0315)**

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

In addition, the following changes have been introduced.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**FRC:** introduction updated.

### **Chlorobutanol (0382)**

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### **Cholecalciferol concentrate (powder form) (0574)**

**Assay:** due to the revision of general chapter 2.2.4. *Approximate pH of solutions*, the wording 'neutral to phenolphthalein' has been replaced.

### **Cholecalciferol concentrate (water-dispersible form) (0598)**

**Assay:** due to the revision of general chapter 2.2.4. *Approximate pH of solutions*, the wording 'neutral to phenolphthalein' has been replaced.

### Citric acid (0455)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Copper sulfate (0893)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Croscarmellose sodium (0985)

This monograph is revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

In addition, the following changes have been introduced.

**Characters:** substance hygroscopic.

**Identification C:** preparation fully described since test for heavy metals deleted.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Sulfated ash:** usual test procedure prescribed to align with harmonised text.

**FRC:** introduction updated.

**Degree of substitution:** volume of indicator increased.

### Cystine (0998)

**Identification:** TLC previously used in test for ninhydrin-positive substances now only used for Identification C.

**Ninhydrin-positive substances:** TLC replaced by chromatography using amino acid analyser that also allows quantification of ammonium.

**Chlorides:** method replaced by more sensitive test.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Impurities:** section added.

### Dexamethasone acetate (0548)

**Content:** limits updated to reflect change in assay method.

**Identification:** TLC in 1<sup>st</sup> identification series replaced by cross-reference to LC for assay.

**Related substances:** new specified impurity introduced.

**Loss on drying:** quantity of substance to be examined increased.

**Assay:** UV absorbance replaced by modified LC for related substances.

### Dimethyl sulfoxide (0763)

**Refractive index:** upper limit modified.

### Diosmin (1611)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Disodium phosphate (1509)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Dobutamine hydrochloride (1200)

**Identification:** 2<sup>nd</sup> identification series deleted as substance not used in pharmacies for extemporaneous preparations.

**Optical rotation:** test deleted as single enantiomer is not available on the market.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Docetaxel (2593)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Dutasteride (2641)

**Related substances test B:** resolution requirement between peaks due to impurities H and I lowered to minimum 1.5, which still allows appropriate separation of these 2 late-eluting impurities.

### Enalapril maleate (1420)

**Related substances:** isocratic step added to gradient; correction factor introduced for impurity H and impurity limits revised based on the quality of currently approved products on the market; due to its high correction factor (around 25), impurity G now quantified using an external standard and with a more concentrated test solution.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Ephedrine (0488)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Ergocalciferol (0082)

**Related substances:** peak-to-valley ratio requirement for separation between impurity A and pre-ergocalciferol lowered to 1.2.

### Ergotamine tartrate (0224)

**Identification C:** TLC not needed in the first identification since infrared spectrophotometry is sufficiently specific.

**Specific optical rotation:** test deleted; the method uses chloroform to extract the base and the test is no longer necessary since the impurities are covered by the new LC.

**Related substances:** TLC replaced by LC, a list of impurities is added to the monograph; TLC now only used for the second identification.

**Appearance of solution:** test deleted.

### Erythromycin (0179)

The text is an outcome of revision proposals published in Pharmeuropa issues 21.3, 24.2 and 26.2.

**Identification:** test B TLC plate updated; tests C and D deleted.

**Specific optical rotation:** test deleted as quality of substance adequately controlled by test for related substances.

**Related substances, Assay:** an improved LC method is introduced with new limits for impurities and for content.

With respect to the Guideline on Setting Specifications for Related Substances in Antibiotics EMA/CHMP/CVMP/QWP/199250/2009 the limits for related substances have been revised and are now formatted as far as is practical with regard to the Guideline, given the known complex nature of the impurity profiles and the feasibility of the analytical method.

A significant change from the previous version of the monograph is that the limit for any other impurity is set at 0.4 per cent as opposed to 3.0 per cent.

A number of individual impurities are now specified at a maximum limit going from 0.4 per cent to 3.0 per cent. A new *erythromycin for system suitability CRS* is used and an additional *erythromycin for impurity M identification CRS* is provided. All other impurities are covered by the limit of 0.4 per cent.

The acceptance criteria for related substances are now expressed quantitatively.

**Impurities:** additional impurities added relating to test for related substances.

### Erythromycin estolate (0552)

The text is an outcome of revision proposals published in Pharmeuropa issues 21.3, 24.2 and 26.2.

**Content:** lower content limit increased.

**Related substances, Assay:** an improved LC method is introduced with new limits for impurities and for content.

With respect to the Guideline on Setting Specifications for Related Substances in Antibiotics EMA/CHMP/CVMP/QWP/199250/2009 the limits for related substances have been revised and are now formatted as far as is practical with regard to the Guideline, given the known complex nature of the impurity profiles and the feasibility of the analytical method.

A significant change from the previous version of the monograph is that the limit for any other impurity is set at 0.4 per cent as opposed to 0.2 per cent.

A number of individual impurities are now specified at a maximum limit going from 0.4 per cent to 3.0 per cent. A new *erythromycin for system suitability CRS* is used. All other impurities are covered by the limit of 0.4 per cent.

The acceptance criteria for related substances are now expressed quantitatively.

**Free erythromycin:** test details harmonised.

**Impurities:** additional impurities added relating to test for related substances.

### Erythromycin ethylsuccinate (0274)

The text is an outcome of revision proposals published in Pharmeuropa issues 21.3, 24.2 and 26.2.

**Content:** lower content limit increased.

**Specific optical rotation:** test deleted as quality of substance adequately controlled by test for related substances.

**Related substances, Assay:** an improved LC method is introduced with new limits for impurities and for content.

With respect to the Guideline on Setting Specifications for Related Substances in Antibiotics EMA/CHMP/CVMP/QWP/199250/2009 the limits for related substances have been revised and are now formatted as far as practical with regard to the Guideline, given the known complex nature of the impurity profiles and the feasibility of the analytical method.

A significant change from the previous version of the monograph is that the limit for any other impurity is set at 0.4 per cent as opposed to 3.0 per cent.

A number of individual impurities are now specified at a maximum limit going from 0.4 per cent to 3.0 per cent, 1 of which is of unknown structure. A new *erythromycin for system suitability CRS* is used and an additional *erythromycin ethylsuccinate for impurity P identification CRS* is provided. All other impurities are covered by the limit of 0.4 per cent.

The acceptance criteria for related substances are now expressed quantitatively.

**Free erythromycin:** test details harmonised.

**Impurities:** additional impurities added relating to test for related substances.

### Erythromycin lactobionate (1098)

The text is an outcome of revision proposals published in Pharmeuropa issues 21.3, 24.2 and 26.2.

**Identification:** tests A, B and C replaced by infrared spectrophotometry using a CRS.

**Related substances, Assay:** an improved LC method is introduced with new limits for impurities and for content.

With respect to the Guideline on Setting Specifications for Related Substances in Antibiotics EMA/CHMP/CVMP/QWP/199250/2009 the limits for related substances have been revised and are now formatted as far as is practical with regard to the Guideline, given the known complex nature of the impurity profiles and the feasibility of the analytical method.

A significant change from the previous version of the monograph is that the limit for any other impurity is set at 0.4 per cent as opposed to 0.2 per cent.

A number of individual impurities are now specified at a maximum limit going from 0.4 per cent to 3.0 per cent. A new *erythromycin for system suitability CRS* is used. All other impurities are covered by the limit of 0.4 per cent.

The acceptance criteria for related substances are now expressed quantitatively.

**Bacterial endotoxins:** test deleted.

**Impurities:** additional impurities added relating to test for related substances.

### Erythromycin stearate (0490)

The text is an outcome of revision proposals published in Pharmedropa issues 21.3, 24.2 and 26.2.

**Content:** lower content limit increased.

**Identification:** TLC test deleted, as infrared absorption spectrophotometry is sufficient.

**Specific optical rotation:** test deleted as quality of substance adequately controlled by test for related substances.

**Related substances, Assay:** an improved LC method is introduced with new limits for impurities and for content.

With respect to the Guideline on Setting Specifications for Related Substances in Antibiotics EMA/CHMP/CVMP/QWP/199250/2009 the limits for related substances have been revised and are now formatted as far as is practical with regard to the Guideline, given the known complex nature of the impurity profiles and the feasibility of the analytical method.

A significant change from the previous version of the monograph is that the limit for any other impurity is set at 0.4 per cent as opposed to 3.0 per cent.

A number of individual impurities are now specified at a maximum limit going from 0.4 per cent to 3.0 per cent, 1 of which is of unknown structure. A new *erythromycin for system suitability CRS* is used and an additional *erythromycin stearate for impurity S identification CRS* is provided. All other impurities are covered by the limit of 0.4 per cent.

The acceptance criteria for related substances are now expressed quantitatively.

**Impurities:** additional impurities added relating to test for related substances.

### Etodolac (1422)

**Related substances:** preparation of reference solution (c) revised to reflect that *etodolac for peak identification CRS* is now produced by evaporation.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Fenofibrate (1322)

**Identification:** IR sample preparation deleted in accordance with current policy.

**Related substances:** limits for impurities A and B and disregard limit updated in line with general monograph *Substances for pharmaceutical use (2034)*.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Fluconazole (2287)

**Related substances:** calculation of total impurities amended as impurities B and C quantified against external standards.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Flupentixol dihydrochloride (1693)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Gliclazide (1524)

**Identification:** method of sample preparation no longer specified.

**Related substances:** limit of impurity F and disregard limit updated in line with general monograph *Substances for pharmaceutical use (2034)*.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Glucose (0177)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Glycerol monolinoleate (1429)

**Assay:** the calculation formulas have been modified to take account of the water and the free glycerol content for the calculation of the content of monoacylglycerols, diacylglycerols and triacylglycerols; free fatty acids co-elute with monoacylglycerols and this is also reflected in the modified calculation formulas; the calculation of the content of each glyceride is now made with respect to the sum of the areas of the peaks due to monoacylglycerols, diacylglycerols and triacylglycerols.

### Glycerol mono-oleate (1430)

**Assay:** the calculation formulas have been modified to take account of the water and the free glycerol content for the calculation of the content of monoacylglycerols, diacylglycerols and triacylglycerols; free fatty acids co-elute with monoacylglycerols and this is also reflected in the modified calculation formulas; the calculation of the content of each glyceride is now made with respect to the sum of the areas of the peaks due to monoacylglycerols, diacylglycerols and triacylglycerols.

### Glycerol monostearate 40-55 (0495)

**Assay:** the calculation formulas have been modified to take account of the water and the free glycerol content for the calculation of the content of monoacylglycerols, diacylglycerols and triacylglycerols; free fatty acids co-elute with monoacylglycerols and this is also reflected in the modified calculation formulas; the calculation of the content of each glyceride is now made with respect to the sum of the areas of the peaks due to monoacylglycerols, diacylglycerols and triacylglycerols.

### Indapamide (1108)

**Impurity C:** LC test added to cover impurity 1-amino-2-methyl indoline; impurity demonstrated to be genotoxic; limit of 600 ppm set according to threshold of toxicological concern (TTC) and daily dosage of 2.5 mg.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Indometacin (0092)

**Definition:** limits for content modified as LC assay now prescribed.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** volumetric titration replaced by LC.

### Lactose (1061)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Lithium carbonate (0228)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** use of the colour indicator has been replaced by a potentiometric end-point determination.

### Lufenuron for veterinary use (2177)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Magnesium citrate (2339)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Nevirapine (2255)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Niclosamide (0679)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

### Norethisterone acetate (0850)

**Content:** limits updated to reflect change in assay method.

**Assay:** titration replaced by LC used for related substances.

### Oxytetracycline dihydrate (0199)

**Identification:** introduction of LC as an alternative to TLC for identification purposes.

**Specific absorbance:** test removed as there is now an LC assay which is sufficient.

**Related substances, Assay:** introduction of an improved method giving better separation, better baseline which is MS compatible and capable of identifying additional impurities. Impurity limits adapted based on batch data.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Sulfated ash:** tightening of limits based on batch data.

**Impurities:** updated to include additional impurities.

### Oxytetracycline hydrochloride (0198)

**Identification:** introduction of LC as an alternative to TLC for identification purposes.

**Specific absorbance:** test removed as there is now an LC assay which is sufficient.

**Related substances, Assay:** introduction of an improved method giving better separation, better baseline which is MS compatible and capable of identifying additional impurities. Impurity limits adapted based on batch data.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Sulfated ash:** tightening of limits based on batch data.

**Impurities:** inclusion of list of specified and unspecified impurities.

### Paroxetine hydrochloride (2283)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Phloroglucinol (2301)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Potassium hydrogen carbonate (1141)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** use of the colour indicator has been replaced by a potentiometric end-point determination.

### Povidone (0685)

This monograph has been revised to indicate its status within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopoeia and the European Pharmacopoeia. A footnote has been included in the text to refer to chapter 5.8. *Pharmacopoeial harmonisation*.

In addition, the following changes have been introduced.

**Definition:** range for nominal K-value included.

**Identification A:** sample size deleted.

**Identification B:** deleted to avoid use of reagent on list of REACH regulation annex XIV.

**Viscosity, expressed as K-value:** symbol  $\eta$  (corresponding to dynamic viscosity) corrected to  $v_{rel}$  to avoid misinterpretation; notion of nominal value range deleted.

**Formic acid:** LC parameters altered: column size, particle size, temperature, mobile phase, flow rate; quantification approach used instead of limit test.

**Impurity A:** LC parameters altered: reference solution, column size, flow rate; quantification approach used instead of limit test; information about washing of column kept for user-friendliness.

**Impurity B:** LC parameters altered: test solution, reference solution, column size, temperature, mobile phase, flow rate; quantification approach used instead of limit test; information about washing of column kept for user-friendliness.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

Editorial changes also made throughout the monograph.

### Propylene glycol monolaurate (1915)

**Assay:** the calculation formulas have been modified to take account of the water content for the calculation of the content of monoesters and diesters; free fatty acids co-elute with monoesters and this is also reflected in the modified calculation formulas.

### Risedronate sodium 2.5-hydrate (2572)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Rosuvastatin calcium (2631)

**Enantiomeric purity:** as an evaporated standard is now used for *impurity G CRS*, the wording of reference solutions (b) and (c) has been updated accordingly.

### Salicylic acid (0366)

**Related substances:** disregard limit updated in line with general monograph *Substances for pharmaceutical use (2034)*.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Sodium ascorbate (1791)

**Impurities:** structure and nomenclature of impurities C and D corrected.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Sodium carbonate (0773)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** use of the colour indicator has been replaced by a potentiometric end-point determination.

### Sodium carbonate decahydrate (0191)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** use of the colour indicator has been replaced by a potentiometric end-point determination.

### Sodium carbonate monohydrate (0192)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** use of the colour indicator has been replaced by a potentiometric end-point determination.

### Sodium hydrogen carbonate (0195)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Assay:** use of the colour indicator has been replaced by a potentiometric end-point determination.

### Sodium sulfite (0775)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Starches, hydroxyethyl (1785)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Sucrose monopalmitate (2319)

**Assay:** the calculation of the content of each glyceride is now made with respect to the sum of the areas of the peaks due to monoesters, diesters and triesters; free fatty acids co-elute with monoesters and this is also reflected in the modified calculation formulas.

### Sucrose stearate (2318)

**Assay:** the calculation of the content of each ester is now made with respect to the sum of the areas of the peaks due to monoesters, diesters and triesters; free fatty acids co-elute with monoesters and this is also reflected in the modified calculation formulas.

### Sumatriptan succinate (1573)

**Identification:** IR sample preparation deleted in accordance with current policy.

**Impurities A and H:** reference solution (b) slightly modified.

**Related substances:** limit for impurity E updated in line with general monograph *Substances for pharmaceutical use (2034)*.

### Tartaric acid (0460)

**Definition:** at the time of monograph elaboration, tartaric acid was obtained from natural sources only; definition therefore updated as the monograph does not cover the synthetic product.

**Oxalic acid:** correct limit is 360 ppm.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Theophylline-ethylenediamine (0300)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Ticlopidine hydrochloride (1050)

**Identification B:** method of sample preparation no longer specified.

**Related substances:** limit for unspecified impurities and disregard limit updated in line with general monograph *Substances for pharmaceutical use (2034)* (maximum daily dose lower than 2 g/day). *Methanol R1* used for the mobile phase.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Tilidine hydrochloride hemihydrate (1767)

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Timolol maleate (0572)

**Related substances:** preparation of reference solution (b) revised to use an individual CRS for impurity F.

### Torsemide (2132)

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

### Triamcinolone hexacetonide (0867)

**Content:** limits updated to reflect change in assay method.

**Characters:** solubility in a lipophilic solvent introduced.

**Identification:** TLC replaced by cross-reference to assay LC.

**Specific optical rotation:** limits updated based on recent batch data.

**Related substances:** 2 additional impurities introduced; limits updated based on recent batch data; explicit criterion for unspecified impurities added in line with general monograph *Substances for pharmaceutical use (2034)*.

**Assay:** UV absorbance replaced by related substances LC.

**Impurities:** section updated.

### Triglycerides, medium-chain (0868)

**Characters:** relative density and refractive index moved from Tests to Characters.

**Identification:** 1<sup>st</sup> and 2<sup>nd</sup> identification series reorganised; Identification A replaced by the test for iodine value; Identification D replaced by a cross-reference to the test for viscosity.

**Iodine value, Saponification value:** tests deleted and moved to Identification section as the monograph already describes a test for composition of fatty acids.

**Unsaponifiable matter:** test deleted as, in view of the manufacturing process, the content of unsaponifiable matter is considered negligible.

**Composition of fatty acids:** indication to use the mixture of calibrating substances in Table 2.4.22.-2 introduced; limit for fatty acids of chain length greater than C<sub>16</sub> introduced in order to ensure that the substance is obtained from coconut oil or palm kernel oil by fractionated distillation followed by esterification with glycerol.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.

**Water:** semi-micro determination replaced by micro determination.

**Total ash:** test replaced by a test for sulfated ash, which is more adapted to this substance (total ash usually used for herbal materials).

### **Valaciclovir hydrochloride (1768)**

**Title:** 'anhydrous' deleted following implementation of the new policy for hydrates.

**Heavy metals:** test deleted in line with Ph. Eur. strategy on elemental impurities.