# Comments concerning revised texts published in the 10th Edition (10.0)

*The following information details the technical modifications that have been made to revised texts adopted by the European Pharmacopoeia Commission at the November 2018 session and published in the 10th Edition (10.0).*

*When a text has been modified, this is indicated by horizontal or vertical lines in the margin of 10.0. 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.*

## GENERAL CHAPTERS

### 2.2.25. Absorption spectrophotometry, ultraviolet and visible

This general chapter has undergone a comprehensive revision, and now also covers UV-Vis detectors for chromatographic systems and process analytical technology applications.

For the purpose of absorbance accuracy, nicotinic acid has been introduced as an alternative to potassium dichromate which is listed in Annex XIV of the REACH regulation.

### 2.6.8. Pyrogens

The text has been clarified, as part of an assessment on the appropriate use of the term ‘precision’ according to the International vocabulary of metrology (VIM).

### 2.6.33. Residual pertussis toxin

General chapter revised in its entirety as follows:

The title of the general chapter has been revised and no longer mentions the test for irreversibility of pertussis toxoid, in line with monographs on acellular pertussis vaccines which are published in the same edition and which no longer require the test.

The histamine sensitisation test in mice (HIST) has been replaced by a standardised CHO cell-clustering assay for residual pertussis toxin testing, based on the results of 2 collaborative studies (cf. “Transferability study of CHO cell clustering assays for monitoring of pertussis toxin activity in acellular pertussis vaccines” published in Pharmeureuropa Bio & Scientific Notes in 2016, and “Calibration of pertussis toxin BRP batch 1 in a standardised CHO cell-based clustering assay” published in Pharmeureuropa Bio & Scientific Notes in 2016).

The specific CHO assay described in the general chapter is intended only for the testing of non-adsorbed purified pertussis components.

## 2.6.35. Quantification and characterisation of residual host-cell DNA

This general chapter describes analytical methods for both the quantification of residual host-cell DNA in biological products produced in cell substrates, and for the characterisation of its size. It focuses on the most widely used techniques, i.e. real-time quantitative PCR and an immunoenzymatic method (the threshold assay). To facilitate the selection of a scientifically sound and reliable method, the characteristics of both methods are summarised and compared.

Based on the conclusions of a previous WHO collaborative study, which explored the sensitivity and reproducibility of assays for the detection of DNA in biologicals derived from continuous cell lines [Biologicals (1992) 20, 73-81], the hybridisation method is not considered sufficiently reproducible and is therefore not described in this general chapter.

## 2.7.2. Microbiological assay of antibiotics

***Diffusion method, turbidimetric method***: the text has been clarified, as part of an assessment on the appropriate use of the term ‘precision’ according to the international vocabulary of metrology (VIM).

## 2.7.23. Numeration of CD34/CD45+ cells in haematopoietic products

The text has been clarified, as part of an assessment on the appropriate use of the term precision according to the International vocabulary of metrology (VIM).

## 2.7.35. Immunonephelometry for vaccine component assay

***Reagents and reference standards***: the text has been clarified, as part of an assessment on the appropriate use of the term ‘precision’ according to the international vocabulary of metrology (VIM).

## 2.8.25. High-performance thin-layer chromatography of herbal drugs and herbal drug preparations

***Preparation of test solution***: volumes in millilitres are now expressed with an additional significant figure.

***Visual evaluation***: descriptor ‘equivalent’ introduced to facilitate the description of HPTLC chromatograms in individual monographs.

## 2.9.1. Disintegration of tablets and capsules

***Apparatus***: description of discs clarified.

## 2.9.20. Particulate contamination: visible particles

Clarification of: the introduction; inspection parameters for coloured glass or plastic containers and for coloured or turbid preparations (e.g. light sources, intensity of illumination, inspection time); label removal.

Transfer to visible-particle-free sample containers for inspection authorised.

Figure redrawn.

### 3.1.13. Plastic additives

The structure for plastic additive 24 has been modified to account for the multi-compound mixture of this additive.

### 3.3.1. Materials for containers for human blood and blood components

This general chapter was moved from Ph. Eur. subsection 3.*1. Materials used for the manufacture of containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.1.1.* to *3.3.1.* and a sentence was added to indicate that this general chapter is published for information.

### 3.3.2. Materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components

This general chapter was moved from Ph. Eur. subsection *3.1. Materials used for the manufacture of containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.1.1.1. (90001)* to *3.3.2.* and a sentence was added to indicate that this general chapter is published for information.

### 3.3.3. Materials based on plasticised poly(vinyl chloride) for tubing used in sets for the transfusion of blood and blood components

This general chapter was moved from Ph. Eur. subsection *3.1. Materials used for the manufacture of containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.1.1.2. (90002)* to *3.3.3.* and a sentence was added to indicate that this general chapter is published for information.

### 3.3.4. Sterile plastic containers for human blood and blood components

This general chapter was moved from Ph. Eur. subsection *3.2. Containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.2.3.* to *3.3.4.*

### 3.3.5. Empty sterile containers of plasticised poly(vinyl chloride) for human blood and blood components

This general chapter was moved from Ph. Eur. subsection *3.2. Containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.2.4.* to *3.3.5.* and a sentence was added to indicate that this general chapter is published for information.

### 3.3.6. Sterile containers of plasticised poly(vinyl chloride) for human blood containing anticoagulant solution

This general chapter was moved from Ph. Eur. subsection *3.2. Containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.2.5.* to *3.3.6.* and a sentence was added to indicate that this general chapter is published for information.

### 3.3.7. Sets for the transfusion of blood and blood components

This general chapter was moved from Ph. Eur. subsection *3.2. Containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.2.6.* to *3.3.7.* and a sentence was added to indicate that this general chapter is published for information.

***Tests***. The use of *water for injections R* has been replaced by *water R* (the use of sterilised water for injections is not considered suitable for testing purposes) ; this change is in accordance with general chapter *3.3.3. Materials based on plasticised poly(vinyl chloride) for tubing used in sets for the transfusion of blood and blood components*.

***Ethylene oxide***. Modernisation of the gas chromatography method. The use of a packed column has been replaced by the use of a capillary column and the use of mass spectrometry for detection and quantification. The method is considered suitable for the following materials: cyclo-olefin polymers (COP) and copolymers (COC), poly(vinyl chloride) (PVC), and polyurethane (PU). The ethylene oxide extraction step is to be adapted to the type of plastic material to be examined in order to maximise the release of ethylene oxide present.

### 3.3.8. Sterile single-use plastic syringes

This general chapter was moved from Ph. Eur. subsection *3.2. Containers* to a new Ph. Eur. subsection *3.3. Containers for human blood and blood components, and materials used in their manufacture; transfusion sets and materials used in their manufacture; syringes*, which was created to group texts on medical devices. Its numbering was changed from *3.2.8.* to *3.3.8*.

***Tests***: the use of *water for injections R* has been replaced by *water R* (the use of sterilised water for injections is not considered suitable for testing purposes).

***Ethylene oxide***. Modernisation of the gas chromatography method. The use of a packed column has been replaced by the use of a capillary column and the use of mass spectrometry for detection and quantification. The method is considered suitable for the following materials: cyclo-olefin polymers (COP) and copolymers (COC), poly(vinyl chloride) (PVC), and polyurethane (PU). The ethylene oxide extraction step is to be adapted to the type of plastic material to be examined in order to maximise the release of ethylene oxide present.

***Silicone oil***: comparison with *silicone oil CRS*.

***Pyrogens***: in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, the test for pyrogens has been replaced by the test for bacterial endotoxins.

***Labelling***: statements have been revised in accordance with the General Notices.

### 5.3. Statistical analysis of results of biological assays and tests

***Combination of assay results***: the formula given to estimate the inter-assay variation has been replaced with a new formula based on the “Hodges and Olkin method”. In addition, editorial amendments have been made to improve the structure and clarity of the text.

### 5.8. Pharmacopoeial harmonisation

With a view to increasing transparency on the texts harmonised by the PDG, it is proposed to stop mentioning the harmonised and non-harmonised items, as well as the local requirements, in this chapter; conversely sign-off coversheets signed off by the PDG will be made available on the EDQM website. This chapter has been revised accordingly.

### 5.21. Chemometric methods applied to analytical data

Minor changes to improve the clarity of the text.

### 5.22. Names of herbal drugs used in traditional Chinese medicine

Table updated to include a new monograph published in the 10th Edition (10.0).

### 5.24. Chemical imaging

Text clarified (see sub-section *2-8*. Resolution), as part of an assessment on the appropriate use of the term ‘precision’ according to the international vocabulary of metrology (VIM).

## DOSAGE FORMS

### Powders, oral (1165)

***Effervescent powders***: a disintegration test has been added.

## VACCINES FOR HUMAN USE

### Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed) (1931)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*, published in the same edition, emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) (2764)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*, published in the same edition, emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Diphtheria, tetanus, pertussis (acellular, component) and haemophilus type b conjugate vaccine (adsorbed) (1932)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*, published in the same edition, emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Diphtheria, tetanus, pertussis (acellular, component) and hepatitis B ( rDNA) vaccine (adsorbed) (1933)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*, published in the same edition, emphasises the need to

validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed) (1934)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*, published in the same edition, emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content) (2329)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356),* published in the same edition, emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Diphtheria, tetanus, pertussis (acellular, component), hepatitis B ( rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2067)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33,* published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*, published in the same edition, emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (2065)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of the safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*, published in the same edition, emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

## Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) (2149)

***Extraneous agents***. The monograph envisaged the use of PCR as an alternative to the tests described in chapter *2.6.16. Tests for extraneous agents in viral vaccines for human use*, whereas the possibility of using molecular biology methods for extraneous agent testing based on a risk assessment has now been introduced in the general chapter *2.6.16* (01/2018:20616). The monograph has been revised accordingly. High-throughput sequencing methods have been mentioned as an additional example of rapid assays.

## Influenza vaccine (whole virion, inactivated, prepared in cell cultures) (2308)

***Extraneous agents***. The monograph envisaged the use of PCR as an alternative to the tests described in chapter *2.6.16. Tests for extraneous agents in viral vaccines for human use*, whereas the possibility of using molecular biology methods for extraneous agent testing based on a risk assessment has now been introduced in the general chapter *2.6.16* (01/2018:20616). The monograph has been revised accordingly. High-throughput sequencing methods have been mentioned as an additional example of rapid assays.

## Pertussis vaccine (acellular, component, adsorbed) (1356)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

In addition, reference to 'reversion' to toxin is no longer made in the text. The notion of 'stable detoxification of the toxin' is considered preferable.

## Pertussis vaccine (acellular, co-purified, adsorbed) (1595)

Monograph revised to reflect replacement of the histamine sensitisation test in mice (HIST) by a standardised CHO cell-clustering assay for residual pertussis toxin testing, as described in the revised general chapter *2.6.33*, published in the same edition.

The test for irreversibility of pertussis toxoid has been deleted, based on the history of safe use of acellular pertussis vaccines and on data confirming that the pertussis toxoid is stable for marketed vaccines. The revised monograph emphasises the need to validate the detoxification process to demonstrate that the toxoid is immunogenic and stably detoxified.

The requirement to test the final lot for residual pertussis toxin has been deleted. Using a CHO assay, testing of the pre-adsorbed bulk (a stage where the antigens are highly concentrated and therefore detection of pertussis toxin is easier) is considered the most effective and robust approach.

The Definition and Labelling sections have also been aligned with the monograph *Pertussis vaccine (acellular, component, adsorbed) (1356)*.

In addition, reference to 'reversion' to toxin is no longer made in the text. The notion of 'stable detoxification of the toxin' is considered preferable.

## Poliomyelitis vaccine (oral) (0215)

***Extraneous agents***. The reference to the tests in adult mice and guinea pigs is no longer appropriate and has been removed, in line with the revised general chapter *2.6.16. Tests for extraneous agents in viral vaccines for human use* (01/2018:20616). In addition, the reference to the test in suckling mice has also been removed. In accordance with the revised general chapter *2.6.16*, the decision to introduce or maintain the test in suckling mice in a testing strategy must be justified by the risk assessment.

## Yellow fever vaccine (live) (0537)

***Extraneous agents***. The reference to the tests in adult mice and guinea pigs is no longer appropriate and has been removed, in line with the revised general chapter *2.6.16. Tests for extraneous agents in viral vaccines for human use* (01/2018:20616).

# VACCINES FOR VETERINARY USE

## Enteric redmouth disease vaccine (inactivated) for rainbow trout (1950)

***Title, Definition***: scope changed to cover enteric red mouth disease vaccine (inactivated) intended for the active immunisation of rainbow trout only.

# IMMUNOSERA FOR HUMAN USE

## Botulinum antitoxin (0085)

***Definition***: the preparation is described in greater detail.

***Identification***: section revised to allow the use of immunochemical methods for identification, as an alternative to the *in vivo* test currently mentioned.

***Potency***: introduction of a general statement promoting the use of alternative methods for potency in the interest of animal welfare, after validation with respect to the $LD_{50}$ assay.

# HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

## Indigo plant leaf (2727)

***Assay***: the preparation of the reference solution has been modified; in addition, the system suitability test has been improved.

# MONOGRAPHS

## Alfacalcidol (1286)

***Related substances***: introduction of a new UHPLC method to allow separation of the new impurity D.

## Aluminium magnesium silicate (1388)

***Acid demand***: test moved from FRC section to Tests section.

## Anticoagulant and preservative solutions for human blood (0209)

***Definition***: as a consequence of the re-numbering of the general chapter *Sterile plastic containers for human blood and blood components*, from *3.2.3* to *3.3.4*, the text containing a reference to this general chapter has been amended.

## Apomorphine hydrochloride hemihydrate (0136)

***Related substances***: quantitative determination of impurities.

## Arachis oil, hydrogenated (1171)

***Unsaponifiable matter***: quantity of test sample added.

***Composition of fatty acids***: the lower limit of palmitic acid decreased to harmonise with monograph on *Arachis oil, refined (0263)* and to allow the use of refined arachis oil containing 5.0 to 7.0 per cent of palmitic acid to manufacture hydrogenated arachis oil. Reagent used to describe stationary phase modified.

***Nickel:*** in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Benserazide hydrochloride (1173)

***Related substances***: preparation of reference solutions simplified; grades of solvents amended in accordance with Technical Guide (2015).

***Water:*** solvent modified in order to achieve a stable electrometric end-point determination.

## Biotin (1073)

***Related substances:*** a peak due to bromide ion might be visible in the chromatogram of the test solution due to the fact that a bromide salt is formed during synthesis and that impurity C is a dibromide salt. The peak due to bromide is disregarded in the test for related substances. The levels of bromide are controlled by the test for sulfated ash and the limit for impurity C.

## Boldine (2971)

***Related substances***: limit for impurity C increased to 1.5 per cent.

## Borage (starflower) oil, refined (2105)

***Brassicasterol***: test moved to Production section.

***Labelling***: section updated.

## Caffeine (0267)

***Related substances***: reagent used to describe stationary phase modified; relative retention values added.

## Caffeine monohydrate (0268)

***Related substances***: in the preparation of reference solution (b), the volumes are expressed using fewer significant figures due to the qualitative use of this solution; reagent used to describe stationary phase modified; relative retention values added.

## Candesartan cilexetil (2573)

Addition of a Production section and of limits for *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities in the Test section.

On 1 February 2019, the EMA published a press release entitled 'Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities' (available here). The monograph on Candesartan cilexetil has been revised to align the Ph. Eur. requirements as far as possible with the CHMP recommendations:

– Companies to review their manufacturing processes so that they do not produce *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities.

– Transition period for companies to make any necessary changes on their manufacturing process during which strict temporary limits on levels of these impurities will apply. Products containing either impurity above these limits or products containing both nitrosamines at whatever level will not be allowed.

– After this transition period, companies will be requested to demonstrate that their products have no quantifiable levels of these impurities (< 0.03 parts per million) in order to exclude the presence of even lower levels of NDEA or NDMA in their products.

As part of a testing programme carried out by the European network of Official Medicines Control Laboratories (OMCLs) on medicinal products containing sartans, the network is developing methods to detect the above-mentioned contaminants in drug substances and medicinal products. Those methods can be found here.

## Carmellose sodium (0472)

***Sodium glycolate***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorus pentoxide has been deleted from this test.

## Carmellose sodium, low-substituted (1186)

***Sodium glycolate***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorus pentoxide has been deleted from this test.

## Carmustine (1187)

***Related substances***: quantitative test by LC introduced.

***Impurity B***: TLC test introduced.

***Impurities***: section updated.

## Castor oil, hydrogenated (1497)

***Composition of fatty acids***: criterion for symmetry factor for peak due to methyl stearate in test solution expanded beyond range given in general chapter *2.2.46*.

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Castor oil, refined (2367)

***Composition of fatty acids***: criterion for symmetry factor for peak due to methyl stearate in test solution expanded beyond range given in general chapter *2.2.46*.

## Castor oil, virgin (0051)

***Composition of fatty acids***: criterion for symmetry factor for peak due to methyl stearate in test solution expanded beyond range given in general chapter *2.2.46*.

## Cellulose, microcrystalline (0316)

***Microbial contamination***: test considered harmonised between the 3 pharmacopoeias (Ph. Eur., JP, USP).

## Cetyl palmitate (1906)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

***Assay***: reagent used to describe stationary phase modified.

## Chlorpromazine hydrochloride (0475)

***Identification***: cell path length note deleted in test B.

***Related substances***: in the preparation of reference solution (a), the volume is expressed using fewer significant figures; reagent used to describe stationary phase modified.

## Chlortalidone (0546)

***Related substances***: impurity J deleted; system suitability criterion modified accordingly.

## Cholesterol for parenteral use (2397)

***Other sterols, Benzoyl ureas***: reagent used to describe stationary phase modified.

***Assay***: a less stringent requirement for the symmetry factor has been introduced and is identical to that in the monograph *Cholesterol (0993)* which has the same assay method.

## Cod-liver oil (type A) (1192)

***Acid value***: quantity of substance to be examined increased to improve the accuracy of the method for oils with a low acid value.

***Iodine value***: as the oil has a high iodine value, the quantity of substance to be examined has been decreased in order to achieve the 50-60 per cent excess as prescribed in general chapter *2.5.4*.

***Unsaponifiable matter***: quantity of substance to be examined increased.

***Stearin***: the instruction to cool the sample before placing it in the iced water has been introduced to improve repeatability.

***Composition of fatty acids***: system suitability requirements aligned with general chapter *2.4.29. Composition of fatty acids in oils rich in omega-3 acids* and made more user-friendly by introducing theoretical response factors for methyl palmitate, methyl stearate, methyl arachidate and methyl behenate and adjusting for the actual weight of these substances. In addition, hexane has been replaced by trimethylpentane in the preparation of the test solution.

***Assay***: reference to rotary evaporator deleted as other equipment or procedures may be used; grades of solvents amended in accordance with Technical Guide (2015).

## Cod-liver oil (type B) (1193)

***Acid value***: quantity of substance to be examined increased to improve the accuracy of the method for oils with a low acid value.

***Iodine value***: as the oil has a high iodine value, the quantity of substance to be examined has been decreased in order to achieve the 50-60 per cent excess as prescribed in general chapter *2.5.4*.

***Unsaponifiable matter***: quantity of substance to be examined increased.

***Stearin***: the instruction to cool the sample before placing it in the iced water has been introduced to improve repeatability.

***Composition of fatty acids***: system suitability requirements aligned with general chapter *2.4.29. Composition of fatty acids in oils rich in omega-3 acids* and made more user-friendly by introducing theoretical response factors for methyl palmitate, methyl stearate, methyl arachidate and methyl behenate and adjusting for the actual weight of these substances. In addition, hexane has been replaced by trimethylpentane in the preparation of the test solution.

***Assay***: reference to rotary evaporator deleted as other equipment or procedures may be used; grades of solvents amended in accordance with Technical Guide (2015).

## Copovidone (0891)

This monograph has been revised within the context of International Harmonisation, a collaboration between the Japanese Pharmacopoeia, the United States Pharmacopeia and the European Pharmacopoeia.

***Identification A***: sample preparation included; comparison with reference spectrum replaced by comparison with reference substance.

***pH***: test added.

***Viscosity, expressed as K-value***: symbol η (corresponding to dynamic viscosity) corrected to $v_{rel}$ to avoid misinterpretation.

***Monomers***: test deleted and replaced by LC test for determination of 1-vinylpyrrolidin-2-one and vinyl acetate (impurities B and C).

***Impurity A (2-pyrrolidone)***: LC parameters altered: concentration and solvent of reference solution, column dimensions, stationary phase, column temperature, flow rate; quantitative expression of acceptance criteria introduced.

***Assay (nitrogen)***: reference to chapter *2.5.9* deleted and procedure described according to stage 3B text.

Editorial changes also made throughout the monograph.

## Cottonseed oil, hydrogenated (1305)

***Composition of fatty acids***: reagent used to describe stationary phase modified.

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Croscarmellose sodium (0985)

***Sodium glycolate***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorus pentoxide has been deleted from this test.

## Desipramine hydrochloride (0481)

***Solubility***: section updated, now also including solubility in heptane.

***Identification***: 2nd identification series deleted.

***Related substances***: TLC replaced by LC, covering 1 new impurity and avoiding the use of potassium dichromate (REACH).

***Impurities***: section added.

## Diacerein (2409)

***Related substances***: in the preparation of reference solution (b), the volume is expressed using fewer significant figures due to the qualitative use of this solution; grades of solvents amended in accordance with Technical Guide (2015).

***Chromium***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Diethylene glycol palmitostearate (1415)

***Water***: test added.

***Assay***: calculation formulae modified to take account of the water content; co-elution of free fatty acids with monoesters also reflected in the modified calculation formulae.

## Ethylene glycol monopalmitostearate (1421)

***Water***: test added.

***Assay***: calculation formulae modified to take account of the water content; co-elution of free fatty acids with monoesters also reflected in the modified calculation formulae.

## Evening primrose oil, refined (2104)

***Brassicasterol***: test moved to Production section.

***Labelling***: section updated.

## Fenoterol hydrobromide (0901)

***Related substances***: reference solutions modified following establishment of new CRS for system suitability which now contains impurity A; grade of water in mobile phase amended in accordance with Technical Guide (2015).

## Fish oil, rich in omega-3 acids (1912)

***Stearin***: the test now specifies that the sample is at room temperature before placing it in the iced water to improve repeatability.

## Follitropin (2285)

***Follitropin oligomers and Assay (Protein):*** the exclusion range of the stationary phase has been adjusted.

***Assay (Potency)***: the text has been clarified, as part of an assessment on the appropriate use of the term “precision” according to the international vocabulary of metrology (VIM).

## Follitropin concentrated solution (2286)

***Follitropin oligomers and Assay (Protein)***: the exclusion range of the stationary phase has been adjusted.

***Assay (Potency):*** the text has been clarified, as part of an assessment on the appropriate use of the term ‘precision’ according to the international vocabulary of metrology (VIM).

## Galactose (1215)

***Related substances***: in the preparation of reference solution (b), volume is expressed using fewer significant figures due to the qualitative use of this solution; grade of solvent in mobile phase amended in accordance with Technical Guide (2015).

***Barium, Lead***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests have been deleted.

## Galantamine hydrobromide (2366)

***Palladium***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Gelatin (0330)

***Identification B:*** incubation temperature revised (2-8 °C instead of 0 °C) to reflect current practice.

## Glycerol dibehenate (1427)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Glycerol distearate (1428)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Glycerol monostearate 40-55 (0495)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Gonadotrophin, chorionic (0498)

***Assay***: the text has been clarified, as part of an assessment on the appropriate use of the term ‘precision’ according to the international vocabulary of metrology (VIM).

## Hard fat (0462)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Hard fat with additives (2731)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Heparin calcium (0332)

***Related substances***: clarifications on chromatogram integration introduced (to disregard any peaks that appear during the initial isocratic step).

## Heparin sodium (0333)

***Related substances***: clarifications on chromatogram integration introduced (to disregard any peaks that appear during the initial isocratic step).

## Human measles immunoglobulin (0397)

***Potency***: the text has been clarified, as part of an assessment on the appropriate use of the term ‘precision’ according to the international vocabulary of metrology (VIM).

## Human plasma for fractionation (0853)

As a consequence of the re-numbering of the general chapter *Sterile plastic containers for human blood and blood components*, from *3.2.3* to *3.3.4*, the text containing a reference to this general chapter has been amended.

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

***Hepatitis A virus antibodies***: the incidence of hepatitis A having decreased in industrialised countries over the previous years, mainly owing to improvements in hygiene and water quality and the availability of an HAV vaccine, anti-HAV titres in large plasma pools used to produce human plasma treated for virus inactivation have decreased as well and therefore the limit for HAV antibodies has been decreased to 0.3 IU/mL.

***Production***: as a consequence of the re-numbering of the general chapter *Sterile plastic containers for human blood and blood components*, from *3.2.3* to *3.3.4*, the text containing a reference to this chapter has been amended.

## Imidacloprid for veterinary use (2924)

***Related substances***: in the preparation of reference solution (c), *acetonitrile R* has been added to dissolve the CRS.

## Infliximab concentrated solution (2928)

***Potency***: preparation of reference solution amended and concentration expressed in IU/mL.

## Irbesartan (2465)

Addition of a Production section and of limits for *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities in the Test section.

On 1 February 2019, the EMA published a press release entitled 'Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities' (available here). The monograph on Irbesartan has been revised to align the Ph. Eur. requirements as far as possible with the CHMP recommendations:

– Companies to review their manufacturing processes so that they do not produce *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities.

– Transition period for companies to make any necessary changes on their manufacturing process during which strict temporary limits on levels of these impurities will apply. Products containing either impurity above these limits or products containing both nitrosamines at whatever level will not be allowed.

– After this transition period, companies will be requested to demonstrate that their products have no quantifiable levels of these impurities (< 0.03 parts per million) in order to exclude the presence of even lower levels of NDEA or NDMA in their products.

As part of a testing programme carried out by the European network of Official Medicines Control Laboratories (OMCLs) on medicinal products containing sartans, the network is developing methods to detect the above-mentioned contaminants in drug substances and medicinal products. Those methods can be found here.

## Lauromacrogol 400 (2046)

***Hydroxyl value***: sample weight modified to improve repeatability of the test and to align with general chapter *2.5.3. Hydroxyl value, Method A*.

## Levodropropizine (1535)

***Related substances***: reagent used to describe stationary phase modified.

***Impurity C***: GC method replaced by more robust HPLC method to avoid interference between peak due to impurity C and peak due to residual solvent methyl isobutyl ketone.

***Enantiomeric purity***: reagent used to describe stationary phase modified.

***Loss on drying***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorus pentoxide has been deleted from this test.

## Losartan potassium (2232)

Addition of a Production section and of limits for *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities in the Test section.

On 1 February 2019, the EMA published a press release entitled 'Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities' (available here). The monograph on Losartan potassium has been revised to align the Ph. Eur. requirements as far as possible with the CHMP recommendations:

– Companies to review their manufacturing processes so that they do not produce *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities.

– Transition period for companies to make any necessary changes on their manufacturing process during which strict temporary limits on levels of these impurities will apply. Products containing either impurity above these limits or products containing both nitrosamines at whatever level will not be allowed.

– After this transition period, companies will be requested to demonstrate that their products have no quantifiable levels of these impurities (< 0.03 parts per million) in order to exclude the presence of even lower levels of NDEA or NDMA in their products.

As part of a testing programme carried out by the European network of Official Medicines Control Laboratories (OMCLs) on medicinal products containing sartans, the network is developing methods to detect the above-mentioned contaminants in drug substances and medicinal products. Those methods can be found here.

## Macrogol 15 hydroxystearate (2052)

***Free macrogols***: grade of solvent in mobile phase amended in accordance with Technical Guide (2015).

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Macrogol 30 dipolyhydroxystearate (2584)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Mesterolone (1730)

***Related substances***: additional specified impurity introduced; explicit criterion for unspecified impurities introduced; system suitability criterion amended; section aligned with requirements in general monograph *Substances for pharmaceutical use (2034)*; grades of solvents amended in accordance with Technical guide (2015).

***Impurities***: section updated.

## Olmesartan medoxomil (2600)

Addition of a Production section and of limits for *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities in the Test section.

On 1 February 2019, the EMA published a press release entitled ‘Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities’ (available here). The monograph on Olmesartan medoxomil has been revised to align the Ph. Eur. requirements as far as possible with the CHMP recommendations:

– Companies to review their manufacturing processes so that they do not produce *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities.

– Transition period for companies to make any necessary changes on their manufacturing process during which strict temporary limits on levels of these impurities will apply. Products

containing either impurity above these limits or products containing both nitrosamines at whatever level will not be allowed.

– After this transition period, companies will be requested to demonstrate that their products have no quantifiable levels of these impurities (< 0.03 parts per million) in order to exclude the presence of even lower levels of NDEA or NDMA in their products.

As part of a testing programme carried out by the European network of Official Medicines Control Laboratories (OMCLs) on medicinal products containing sartans, the network is developing methods to detect the above-mentioned contaminants in drug substances and medicinal products. Those methods can be found here.

## Oxytetracycline hydrochloride (0198)

***Related substances***: the test has been revised in order to include impurity F as specified impurity, present in current batches at levels above the limit for any other impurity; limit for the sum of impurities D, E and F has been introduced.

## Palmitic acid (1904)

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Penicillamine (0566)

***Impurity B***: the text has been clarified, as part as an assessment on the appropriate use of the term ‘precision’ according to the International vocabulary of metrology (VIM).

***Mercury***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

***Loss on drying***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorous pentoxide has been deleted from this test.

## Phenylpropanolamine hydrochloride (0683)

***Identification***: preparation deleted from identification test B; test D deleted.

***Related substances***: TLC replaced by LC, now covering 5 new unspecified impurities; TLC kept for identification test C only.

***Phenylpropanonamine***: test deleted since the new related substances test covers impurities with a benzoyl group.

***Impurities***: section updated.

## Phytomenadione, racemic (3011)

***Related substances***: only the peak due to trans-phytomenadione isomers is visible in the chromatogram obtained with reference solution (c). To quantify impurities accurately, the content of *trans*-phytomenadione isomers as determined in the assay has to be taken into account in the calculation of the percentage content of impurities.

## Propranolol hydrochloride (0568)

***Characters***: the solubility in a lipophilic solvent has been added.

***Related substances***: specifications updated to reflect current quality of substances in approved medicinal products on European market; section aligned with requirements in general monograph *Substances for pharmaceutical use (2034)*.

***Impurities***: section updated.

## Propyl gallate (1039)

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

***Related substances***: TLC test for gallic acid (impurity A) replaced by LC test for related substances and limit for impurity A tightened; TLC now only used for Identification C.

***Assay***: UV replaced by LC method used for the test for related substances.

***Impurities***: section updated.

## Propylene glycol monopalmitostearate (1469)

***Water***: test added.

***Assay***: calculation formulae modified to take account of the water content; co-elution of free fatty acids with monoesters also reflected in the modified calculation formulae.

## Protamine sulfate (0569)

***Definition***: the scope of the monograph has been restricted to protamine sulfate from Salmonidae species. Following the introduction of the LC assay, an acceptance criterion for the content of protamine has been introduced.

***Identification***: a reference to the related substances test and requirements for the principal peaks and the content of the 4 protamine peptides have been introduced. Consequently, the less-specific Identification tests A (specific optical rotation), C (reaction with α-naphthol) and D (reaction with mercuric sulfate) have been deleted. The reference to the precipitation reaction (a) for sulfates of general chapter *2.3.1. Identification reactions of ions and functional groups* has been replaced with a reference to the quantitative test for sulfate of the monograph.

***Related substances***: an LC method for verification of substance purity has been introduced.

***Assay***: an LC method for calculation of protein content has been introduced.

***Mercury***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test for mercury has been deleted. The deletion of the test is supported by batch data from manufacturers.

***Nitrogen***: following the introduction of the LC assay for calculation of protein content, the test has been deleted.

***Bacterial endotoxins***: the test has been deleted in line with the Ph. Eur. policy on *bacterial endotoxins in substances for pharmaceutical use (2015)*.

## Pyridoxine hydrochloride (0245)

***Related substances***: grade of solvents amended in accordance with Technical Guide (2015); correction factor for impurity B deleted; in the preparation of reference solution (b), the volume is expressed using fewer significant figures due to the qualitative use of this solution; limits now expressed in a quantitative way.

## Safflower oil, refined (2088)

***Brassicasterol:*** test moved to Production section.

## Sodium starch glycolate (type A) (0983)

***Sodium glycolate***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorus pentoxide has been deleted from this test.

## Sodium starch glycolate (type B) (0984)

***Sodium glycolate***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorus pentoxide has been deleted from this test.

## Sodium starch glycolate (type C) (1566)

***Sodium glycolate***: subsequent to the revision of general method *2.2.32*, the reference to diphosphorus pentoxide has been deleted from this test.

## Solutions for organ preservation (1264)

***Definition***: as a consequence of the re-numbering of the general chapter *Sterile single-use plastic syringes*, from *3.2.8* to *3.3.8*, the text containing a reference to this general chapter has been amended.

## Soya-bean oil, hydrogenated (1265)

***Composition of fatty acids***: reagent used to describe stationary phase modified.

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Soya-bean oil, refined (1473)

***Brassicasterol***: test moved to Production section.

## Squalane (1630)

***Assay***: reagent used to describe stationary phase modified.

***Nickel***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Sucralfate (1796)

***Arsenic***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Terbutaline sulfate (0690)

***Content***: limits updated in view of available batch data.

***Characters***: solubility in lipophilic solvent added.

***Related substances***: specifications updated to reflect current quality of substances in approved medicinal products on market; explicit criterion for unspecified impurities introduced in accordance with general monograph *Substances for pharmaceutical use (2034)*; grades of solvents amended in accordance with Technical Guide (2015).

***Impurities***: transparency list updated.

## Tilidine hydrochloride hemihydrate (1767)

***Identification***: IR reference spectrum replaced by CRS.

***Related substances***: limits updated in view of recent batch data; new impurity introduced.

***Bacterial endotoxins***: test removed, as the requirements are covered by the general monograph *Substances for pharmaceutical use (2034)*. Refer to Ph. Eur. policy on bacterial endotoxins February 2015 (cf. Pharmeuropa Technical information).

## Triglycerides, medium-chain (0868)

***Chromium, Copper, Lead, Nickel, Tin***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the tests have been deleted as the relevant elemental impurities are considered to originate from the production process.

## Urofollitropin (0958)

***Assay***: the text has been clarified, as part of an assessment on the appropriate use of the term ‘precision’ according to the international vocabulary of metrology (VIM).

## Urokinase (0695)

***Pyrogens***: data supporting replacement of the test with the bacterial endotoxin test has previously been collected. However, in accordance with the *European Pharmacopoeia policy on bacterial endotoxins in substances for pharmaceutical use (2015)*, this aspect is now covered in the general monograph *Substances for pharmaceutical use (2034)*. Consequently, the test for pyrogens has been deleted.

## Valsartan (2423)

Addition of a Production section and of limits for *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities in the Test section.

On 1 February 2019, the EMA published a press release entitled ‘Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities’ (available here). The monograph on Valsartan has been revised to align the Ph. Eur. requirements as far as possible with the CHMP recommendations:

– Companies to review their manufacturing processes so that they do not produce *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) impurities.

– Transition period for companies to make any necessary changes on their manufacturing process during which strict temporary limits on levels of these impurities will apply. Products containing either impurity above these limits or products containing both nitrosamines at whatever level will not be allowed.

– After this transition period, companies will be requested to demonstrate that their products have no quantifiable levels of these impurities (< 0.03 parts per million) in order to exclude the presence of even lower levels of NDEA or NDMA in their products.

As part of a testing programme carried out by the European network of Official Medicines Control Laboratories (OMCLs) on medicinal products containing sartans, the network is developing methods to detect the above-mentioned contaminants in drug substances and medicinal products. Those methods can be found here.

## Vigabatrin (2305)

***Impurity D***: test deleted, as impurity now controlled by modified Related substances test.

***Related substances***: new, more robust method introduced.

## Vinorelbine tartrate (2107)

***Silver***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities, the test has been deleted as the relevant elemental impurity is considered to originate from the production process.

## Wheat starch (0359)

This draft corresponds to Revision 3 Stage 3B within the Pharmacopoeial harmonisation process (Ph. Eur., JP, USP).

Compared to the monograph published in the 9th Edition of the Ph. Eur., the following changes have been included:

***Total protein***: titanium dioxide used instead of selenium and glucose no longer used in the blank test; sample size decreased and solvent volumes adapted.

## Wheat-germ oil, refined (1379)

***Identification***: reference to the test for composition of fatty acids has been added as first identification since it is more specific than the identification of fatty oils by TLC; the latter has been maintained in the 2nd identification series.

***Brassicasterol***: the test has been moved to the Production section.

## Wheat-germ oil, virgin (1480)

***Identification***: reference to the test for composition of fatty acids has been added as first identification since it is more specific than the identification of fatty oils by TLC; the latter has been maintained in the 2nd identification series.

***Brassicasterol***: the test has been moved to the Production section.