# Comments concerning texts published in Supplement 11.5

*Brief descriptions of the modifications that have been made to new, revised and corrected texts adopted by the European Pharmacopoeia Commission at the June session and published in Supplement 11.5 are provided below. Please note that these descriptions are not provided systematically for new and corrected texts, but are instead provided on a case-by-case basis. This information is reproduced in the Knowledge database under View history.*

*All revised, corrected or deleted parts of a text published in the online version of the European Pharmacopoeia are now indicated by change marks in the form of triangles. For reasons of readability, these triangles are not shown in the print version, but users will still be able to determine if a text has been corrected or revised from the version date indicated above the title of the monograph and, if applicable, by 'corrected X.X', indicating publication of a corrected version in Supplement X.X.*

## GENERAL CHAPTERS

### 2.2.25. Absorption spectrophotometry, ultraviolet and visible

***Limit of stray light***. The text has been modified to state that the test for the limit of stray light is not applicable for detectors used in chromatographic systems, after several instrument manufacturers reported that this test is not performed during qualification of equipment in the implementing laboratories. Stray light does not pose a concern for detectors in chromatographic systems because chromatographic signals do not have high absorbance values. Moreover, the recommended minimum absorbances that should be obtained in the test exceed the dynamic range of many detectors.

### 2.2.42. Density of solids

The theoretical density classification based on intra- and interparticulate pores has been introduced. The term 'material density', which covers semi-crystalline and amorphous materials, has been added. The term 'true density' is avoided in this general chapter as it is used inconsistently in the current literature: while it initially applied to crystalline substances only, in some sources it now also includes polymorphic forms.

Various densities are defined and linked with the experimental techniques by which they are determined. The definition of crystal density has been revised.

### 2.2.55. Peptide mapping

This text corresponds to the sign-off text signed by the Pharmacopoeial Discussion Group (PDG). The coordinating pharmacopoeia is the USP. Non-harmonised attributes are placed between black diamonds (♦♦), while local requirements only present in the Ph. Eur. text are placed between white diamonds (◊◊).

Compared to the general chapter published in the Supplement 11.2 of the Ph. Eur., the following changes are included:

This chapter has undergone a general revision to take into account recent developments and current practice in the field of peptide mapping.

Clarification is provided regarding the scope of the general chapter, which focuses on the use of peptide mapping as an identity test, although other possible applications of peptide mapping are acknowledged.

The major steps in developing a peptide mapping procedure (i.e. sample pretreatment, selective cleavage of the peptide bonds (digestion), peptide separation, detection and data analysis) are given in dedicated sections, the content of which has been updated with recent methods, including new liquid chromatographic separation techniques and mass spectrometry detection. In addition, a flow chart has been added to outline the steps and decisions when developing a peptide mapping procedure (Figure 2.2.55-1.).

Finally, the section on validation has been restructured and now contains detailed guidance on the specificity, precision and robustness elements of the analytical validation protocol. A section describing several aspects to be considered prior to validation of a peptide mapping procedure, including guidance on the development of system suitability criteria, has been introduced.

## 2.6.27. Microbiological examination of cell-based preparations

***Growth promotion test***: harmonisation of the incubation time with general chapter *2.6.1. Sterility*.

The incubation time of the growth promotion test has been changed to “not more than 3 days in the case of bacteria and not more than 5 days in the case of fungi” because:

- collaborative studies and data from the literature indicate that B. fragilis grows within 3 days;

- general chapter *2.6.1* states that the other strains of micro-organisms listed in “Table 2.6.27.-1”. – Micro-organisms used for growth promotion test” are to be incubated for not more than 3 days for bacteria and not more than 5 days for fungi.

## 2.6.30. Monocyte-activation test

***Definition (section 2)***. The limit of detection (LOD) has been replaced by test sensitivity in the calculation of the maximum valid dilution (MVD). Test sensitivity is defined as the lowest endotoxin reference standard concentration on the standard curve whose response exceeds the cut-off value; it is an actual point on the standard curve rather than a calculated value. Replacing the LOD with test sensitivity allows a consistent calculation of the MVD and a better comparability between different monocyte-activation test (MAT) setups.

***General procedure (section 3)***. The requirement to use human peripheral blood that is ‘preferably not more than 4 h old’ has been modified to allow its use ‘within a validated timeframe’ since it is difficult for manufacturers to meet the 4 h cut-off point when manufacturing large batches.

The text has been revised to permit the use of anticoagulants other than heparin to prevent the coagulation of human peripheral blood.

***Qualification of cells (section 5-4)***.
- Requirements for pools: the requirement concerning the number of donors for pools has been simplified (pools must consist of donations from a minimum of 4 individual donors). Requirements regarding the number of donors and the volume to be taken from

each donation have been moved to sections 5-1 Whole blood and 5-2 Peripheral blood mononuclear cells (PBMC).

- Information on how the averaging effect may be evaluated, when cells are pooled, has been added.

- Qualification of fresh cells: the scope of section 5-4 has been changed; the section now describes the qualification of fresh cells (complementing section 5-5 on the qualification of cryopreserved cells).

The example range of concentrations for the standard curve generated during qualification has been deleted, as it may vary substantially depending on the test setup and purpose.

***Qualification of cryopreserved cells (section 5-5)***. Information on how the averaging effect may be evaluated, when cells are pooled, has been added.

***Monocytic continuous cell lines (section 5-6)***. The statement that 'monocytic cell lines (…) have limited use for the detection of non-endotoxin pyrogens' has been revised to clarify that cell lines meeting the requirements of section 5-6 are appropriate for the detection of endotoxins and non-endotoxin pyrogens, after successful qualification.

Verifying the functionality/signalling of cell receptors is considered to be necessary as part of assessing the functional stability of a cell line. The text has been adapted accordingly.

***Assurance of criteria for the endotoxin standard curve (section 6-1)***.

The revised general chapter allows the use of non-linear regression models (e.g. 4-/5-parameter logistic model), depending on the number of endotoxin concentrations prepared and the dose-response relationship observed.

Method A required a parallel behaviour of the product dilutions versus the standard curve. It was very unlikely that this requirement would be met for each test, especially if non-endotoxin pyrogens were present. Requirements for linearity and parallelism, considered too strict and often difficult to meet, have been relaxed and deleted, respectively. The validity of the standard curve is ensured by a good fit between data points and the chosen regression model, which may be evaluated visually or through a lack-of-fit test, and a coefficient of determination > 0.975.

Recommendations on the number of data points which may be used for linear and non-linear regression models have been added.

***Test for interfering factors (section 6-2)***. The section has been split into two separate sections: section 6-2 covers the test for interfering factors, applicable to Method 1, whereas section 6-3 covers the determination of the optimal dilutions of the test and reference lots, applicable to Method 2.

- Test for interfering factors (Method 1): spiking with 2x LOD in Method B was considered to be too low to enable spike recovery in the range of 50-200 per cent. The spike concentration for Method 1 is equal to or near the middle of the endotoxin standard curve.

- Determination of the optimal dilutions of the test and reference lots (Method 2): a dilution factor is no longer specified.

***Method validation for non-endotoxin contaminants (section 6-5)***. The validation of the test system for the detection of non-endotoxin contaminants is conducted using non-endotoxin ligands. If available, historic batches found to be contaminated with non-endotoxin contaminants that caused a positive reaction in the rabbit pyrogen test or adverse reactions in humans should also be included. The text has been adapted accordingly. A new sentence

has been added to stress that the test system should, at a minimum, ensure the detection of TLR-4 and 2 other TLR ligands that reflect the most likely contaminants of the preparation tested.

An acceptance criterion of 50-200 per cent has been introduced for spike recovery of non-endotoxin ligands used to validate the test system. The acceptance criterion allows for the spike recovery to exceed 200 per cent where there is synergism between a non-endotoxin ligand and the test solution.

***Method (section 7)***. Methods A and B have been merged into a single semi-quantitative test, referred to as 'Method 1'. Method C is now referred to as 'Method 2'.

***Method 1 - Test procedure (section 7-1-1)***.

- Solutions A, B and C: in Method 1, a specific dilution factor is not imposed for solutions B and C – the dilution is chosen after reviewing the data from the product-specific validation. An example of dilution is provided.

- Solutions AS, BS and CS: in Method 1, standard endotoxin at a concentration equal to or near the middle of the endotoxin standard curve is added to prepare spiked test solutions AS, BS and CS.

***Calculation and interpretation (section 7-1-2)***.
The test is not valid unless at least one of the dilutions displays a spike recovery within 50-200 per cent. The preparation to be examined complies with the test if the mean concentrations of endotoxin equivalents measured in the replicates of solutions A, B and C, after correction for dilution and concentration, are all below the contaminant limit concentration (CLC). The preparation to be examined does not comply with the test if the mean concentration of any of the solutions exceeds the CLC, regardless of the spike recovery.

***Method 2 (section 7-2)***. Criteria for selection of a suitable reference lot have been included. The ratio given as an example has been removed.

***Guidance notes***

- Information regarding the choice of methods: the text has been updated to reflect the replacement of Methods A and B by Method 1.

- Expression of concentrations and product dilutions: new section added, providing recommendations on how to express endotoxin-equivalent concentrations in the MAT and explaining how using concentrations per sample or per well impacts the reported test sensitivity value.

- Information regarding cryoprotectants: section deleted (information considered too detailed for the general chapter).

This revision is also part of a broader exercise aimed at suppressing the rabbit pyrogen test from the Ph. Eur. (see also: https://www.edqm.eu/en/news/european-pharmacopoeia-put-end-rabbit-pyrogen-test). In this context, references to the rabbit pyrogen test have been removed from the Introduction and from the Guidance notes.

## 2.6.40. Monocyte-activation test for vaccines containing inherently pyrogenic components

This new general chapter describes the use of the Monocyte-activation test (MAT) to monitor the consistent pyrogenicity of vaccines containing inherently pyrogenic components.

The MAT as described in the existing chapter *2.6.30. Monocyte-activation test* is primarily intended as a safety test for the measurement of pyrogenic contaminants. For vaccines containing inherently pyrogenic components, the MAT can also serve as a test to monitor production consistency, by controlling the consistent pyrogenicity of the vaccine.

The new chapter complements chapter *2.6.30* and aims at fostering and facilitating the implementation of the MAT for inherently pyrogenic vaccines by providing a method and specific considerations on how to apply the MAT for those vaccines.

### 2.7.5. Assay of heparin

Clarification added concerning the possibility of adjusting volumes in order to use automated methods.

### 2.9.9. Measurement of consistency by penetrometry

The dimensions of the cone presented in Figure 2.9.9.-2 have been updated to be consistent with those given in ISO 2137:2020.

### 2.9.34. Bulk density of powders

This text corresponds to the sign-off text signed by the Pharmacopoeial Discussion Group (PDG). The coordinating pharmacopoeia is the European Pharmacopeia. Non-harmonised attributes are placed between black diamonds (♦♦), while local requirements only present in the Ph. Eur. text are placed between white diamonds (◊◊).

Compared to the general chapter published in the 11th Edition of the Ph. Eur., the following changes are included.

A new classification of bulk density has been introduced with two subcategories ‘Untapped bulk density’ and ‘Tapped bulk density’. The title has been adapted to reflect this change.

***Untapped bulk density, method 2***: the dimensions have been aligned to comply with both ISO 3923-2:1981 and ASTM B329-14.

***Tapped bulk density, method 3***: requirements for replicate determinations have been aligned with methods 1 and 2.

The wording has been clarified in several parts of the text.

### 2.9.36. Powder flow

This text corresponds to the sign-off text signed by the Pharmacopoeial Discussion Group (PDG). The coordinating pharmacopoeia is the European Pharmacopeia. Non-harmonised attributes are placed between black diamonds (♦♦), while local requirements only present in the Ph. Eur. text are placed between white diamonds (◊◊).

Compared to the general chapter published in the 11th Edition of the Ph. Eur., the following changes are included.

The text has been revised to reflect the new classification introduced in general chapter *2.9.34. Bulk density of powders*, which now refers to ‘untapped bulk density’ and ‘tapped bulk density’.

***Shear cell methods***: translational and rotational shear cells have been described as main classes.

The wording has been clarified in several parts of the text.

### 2.9.50. Particle size analysis by dynamic light scattering

This text corresponds to the sign-off text signed by the Pharmacopoeial Discussion Group (PDG). The coordinating pharmacopoeia is the Japanese Pharmacopoeia.

### 5.8. Pharmacopoeial harmonisation

***Pharmacopoeial harmonisation***

The wording has been revised to take into account that the Pharmacopoeial Discussion Group (PDG) has more than 3 members.

### 5.15. Functionality-related characteristics of excipients

***Physical grades***: as the title of general chapter *2.9.34* has been changed to "*Bulk density of powders*", the reference to the chapter has been modified accordingly.

***Pharmacopoeial harmonisation***: the wording has been revised to take into account that the Pharmacopoeial Discussion Group (PDG) may have more than 3 members.

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

Table updated to include 1 new monograph.

## GENERAL MONOGRAPHS

### Pharmaceutical preparations (2619)

In exceptional cases, based on scientific, technical and regulatory considerations, limits for related substances that are wider than those set in a monograph on a medicinal product containing one or more chemically defined active substances can be deemed appropriate, and approving such limits may be necessary to ensure the quality and availability of the product. Such cases have to be justified by the applicant and approved by a competent authority, and shall be brought to the attention of the Ph. Eur. Commission. Consequently, a new paragraph Related Substances has been added in the TESTS section.

## HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

### Amomum fruit (2554)

***Definition***: botanical name updated.

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

***Identification C***: analytical procedure improved, harmonised with that of *Round amomum fruit (2555)* and aligned with general chapter *2.8.25*.

### Centaury (1301)

***Definition***: Centaurium majus and C. suffruticosum deleted as covered by referencing sensu lato; number of synonyms listed reduced to two in order to keep the most commonly used.

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

### Round amomum fruit (2555)

***Definition***: botanical name updated.

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

***Identification C***: analytical procedure improved, harmonised with that of *Amomum fruit (2554)* and aligned with general chapter *2.8.25*.

### Szechwan lovage rhizome (2634)

***Definition***: Botanical name updated.

***Loss on drying***: test replaced by determination of water by distillation (*2.2.13*); proposed specification set based on recent batch data.

## HOMOEOPATHIC PREPARATIONS

### Homoeopathic preparations (1038)

The general monograph *Methods of preparation of homoeopathic stocks and potentisation (2371)* has been revised to add a new method (*5.3*) describing the Korsakovian method of manufacture (single-flask potentisation method). The monograph *Homeopathic preparations (1038)* has been revised accordingly to take this new method into account.

***Potentisation***: a sentence has been added to describe the new designation ‘K’ and the potentisation steps for the newly added Korsakovian dilutions.

***Dosage forms***: in the paragraph on ‘Manufacturing methods’ it is now clarified that the multiple-flask potentisation method is used unless otherwise stated to avoid any confusion due to the newly introduced single-flask potentisation method.

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

The general chapter has been revised to add a new method (*5.3*) describing the Korsakovian method of manufacture (single-flask potentisation method). All other methods describe multiple-flask potentisation, but do not expressively state this fact. Therefore to avoid any confusion due to the newly introduced single-flask potentisation method, it is now clarified that the multiple-flask potentisation method is used unless otherwise stated, as in method *5.3*.

The wording and the layout used throughout the monograph have been harmonised for greater clarity, in particular to specify the corresponding general method numbers after “loss on drying” (*2.2.32*) or “water content” (*2.2.13*) and for the use of the sub-headline: “Adjustment to any value specified in the individual monograph”.

Moreover, a note explaining the use of inverted commas in Potentisation subchapters has been included.

### Homoeopathic pillules, coated (2786)

Some instances of “syrup” and “mixture” changed to “sucrose syrup” and “coating preparation” for greater clarity.

***Mixtures***. Ratio of quantities of sucrose syrup and purified water changed to reflect products currently on the European market.

Further explanatory details to the subchapters of this monograph are given below:

***Aqueous dilutions***. One aqueous dilution is mixed with sucrose syrup and potentised (not to be confused with the “Mixtures” section), then this is used for coating.

***Triturations***. One trituration is only mixed with sucrose syrup (not to be confused with the “Mixtures” section), then this is used for coating.

***Mixtures***. Different kinds of homoeopathic preparations (e.g. two dilutions or one dilution and one trituration) are mixed together (current term “mixtures”) and then purified water and sucrose syrup are added. Then this is used for coating.

The homoeopathic preparations are co-potentised with sucrose syrup according to method *5.1.2* of monograph *2371* in a separate, previous step. This co-potentised mixture (to which purified water and sucrose syrup still have to be added) already contains a certain amount of sucrose. This is taken into account when using the given calculations for the required composition of the coating preparation.

## MONOGRAPHS

### Acamprosate calcium (1585)

***Identification***: test B modified in order to avoid the use of chloroform.

### Aluminium oxide, hydrated (0311)

***Arsenic***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), the test has been deleted.

### Aluminium sodium silicate (1676)

***Arsenic, Lead***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), the tests have been deleted.

### Calcium hydrogen phosphate (0981)

***Functionality-related characteristics***: in line with revised general chapter *2.9.34, “Bulk and tapped density”* has been changed to “*Bulk density of powders*”.

### Calcium hydrogen phosphate dihydrate (0116)

***Functionality-related characteristics***: in line with revised general chapter *2.9.34*, “*Bulk and tapped density*” has been changed to “*Bulk density of powders*”.

## Calcium phosphate (1052)

***Functionality-related characteristics***: in line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*".

## Calcium sulfate dihydrate (0982)

***Identification C***: *chloroform R* has been replaced by *methylene chloride R* in reaction (a) of calcium.

***Functionality-related characteristics***: in line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*".

## Copovidone (0891)

***Functionality-related characteristics***: in line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*".

## Flunitrazepam (0717)

***Related substances***: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; system suitability amended.

***Sulfated ash***: use of platinum crucible introduced due to the presence of fluoride in the API.

***Impurities***: section has been updated.

## Haloperidol decanoate (1431)

***Related substances***: impurities specifications updated to reflect the quality of substances in approved medicinal products on the European market; system suitability amended.

## Heparin calcium (0332)

***Production***: The figure of 0.1 per cent for the capability of the method used to identify the presence of material from other species has been deleted because it was often misinterpreted as the acceptance criterion for the maximum amount of ruminant material in the tested material. The requirement for the absence of contaminant species has been emphasised. A limit of detection of at least 1000-fold lower than the determined amount of porcine DNA has been introduced for PCR-based methods serving as established surrogate methods. The need to apply the test at the stage in the process where DNA is still present in sufficient amounts has been emphasised.

***Related substances***: The reagent used to describe the stationary phase has been modified.

## Heparin sodium (0333)

***Production***: The figure of 0.1 per cent for the capability of the method used to identify the presence of material from other species has been deleted because it was often misinterpreted as the acceptance criterion for the maximum amount of ruminant material in the tested material. The requirement for the absence of contaminant species has been emphasised. A limit of detection of at least 1000-fold lower than the determined amount of porcine DNA has been introduced for PCR-based methods serving as established surrogate methods. The need to apply the test at the stage in the process where DNA is still present in sufficient amounts has been emphasised.

***Related substances***: The reagent used to describe the stationary phase has been modified.

## Isosorbide dinitrate, diluted (1117)

***Definition***: chemical name moved from 'content' to the definition of the composition. Identification:

*- test B: TLC silica gel G plate R replaced with TLC silica gel plate R;*

*- test C: modified in order to avoid the use of ethylene chloride R (REACH); TLC silica gel G plate R replaced by TLC silica gel plate R;*

*- test D: in line with the revision of general method 2.2.32, the reference to diphosphorus pentoxide has been deleted.*

## Isosorbide mononitrate, diluted (1118)

***Definition***: chemical name moved from 'content' to the description of the composition.

***Identification***:

*- test B: TLC silica gel G plate R replaced with TLC silica gel plate R;*

*- test C: mobile phase modified in order to avoid the use of ethylene chloride R (REACH); TLC silica gel G plate R replaced by TLC silica gel plate R;*

*- test D: in line with the revision of general method 2.2.32, the reference to diphosphorus pentoxide has been deleted.*

## Lactose (1061)

***Functionality-related characteristics***: in line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*". Untapped bulk density, tapped bulk density and the Hausner ratio are all mentioned in the revised chapter and therefore no longer need to be mentioned explicitly in this monograph.

## Lactose monohydrate (0187)

***Functionality-related characteristics***: In line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*". Untapped bulk density, tapped bulk density and the Hausner ratio are all mentioned in the revised chapter and therefore no longer need to be mentioned explicitly in this monograph.

## Magnesium carbonate, heavy (0043)

***Identification A***: In line with revised general chapter *2.9.34* which provides a new classification of bulk density and introduces a new term, "untapped bulk density", the text now specifies that the "Untapped bulk density" is to be measured.

***Functionality-related characteristics***: In line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*".

## Magnesium carbonate, light (0042)

***Identification A***: In line with revised general chapter *2.9.34* which provides a new classification of bulk density and introduces a new term, "untapped bulk density", the text now specifies that the "Untapped bulk density" is to be measured.

***Functionality-related characteristics***: In line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*".

## Magnesium oxide, heavy (0041)

***Identification A***: In line with revised general chapter *2.9.34* which provides a new classification of bulk density and introduces a new term, “untapped bulk density”, the text now specifies that the “Untapped bulk density” is to be measured.

***Functionality-related characteristics***: In line with revised general chapter *2.9.34*, “*Bulk and tapped density*” has been changed to “*Bulk density of powders*”.

## Magnesium oxide, light (0040)

***Identification A***: In line with revised general chapter *2.9.34* which provides a new classification of bulk density and introduces a new term, “untapped bulk density”, the text now specifies that the “Untapped bulk density” is to be measured.

***Functionality-related characteristics***: In line with revised general chapter *2.9.34*, “*Bulk and tapped density*” has been changed to “*Bulk density of powders*”.

## Magnesium peroxide (1540)

***Arsenic***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), the test has been deleted.

## Magnesium trisilicate hydrate (0403)

***Title***: hydration form identified in the title according to current policy on hydrates.

***Arsenic***: in line with the Ph. Eur. implementation strategy for the ICH Q3D guideline on elemental impurities (please see Press release), the test has been deleted.

## Mefloquine hydrochloride (1241)

***Related substances***: test improved and updated with a different column and mobile phase; changed to quantitative style; limits updated: impurity C is the only specified impurity and is used for system suitability.

***Water***: less accurate sample size in accordance with Technical Guide.

## Morphine hemisulfate 2.5-hydrate (1244)

***Title***: title revised to add degree of hydration in accordance with Ph. Eur. policy.

***Identification***: one reaction of sulfates is sufficient.

***Related substances***: quantitative style used for the calculation of impurities.

## Morphine hydrochloride trihydrate (0097)

***Title***: revised to add degree of hydration in accordance with Ph. Eur. policy.

***Identification A***: use of reference spectrum as an alternative to CRS added.

***Related substances***: quantitative style used for the calculation of impurities.

## Nadroparin calcium (1134)

The following changes in specifications have been made as a consequence of the introduction of a Broad Standard Table calibration method for determination of molecular

mass distribution in the monograph *Heparins, low molecular mass (0828)* in Supplement 9.8, which affected these parameters:

***Definition***: The requirements for the values for the mass-average relative molecular mass ranges and the characteristic value for nadroparin calcium have been amended.

***Identification***: The requirements for the values for mass percentage of chains in the 2000-8000 and 2000-4000 ranges as well as below 2000 have been amended.

## Norgestrel (0940)

***Identification***: labels of the tests updated; reference spectrum replaced by reference substance in IR identification; description of optical rotation test moved under Tests section in line with Technical guide (2022).

***Optical rotation***: test added to Tests section and its description transferred from Identification section; concentration of solution used in the measurement of the angle of optical rotation adjusted to ensure complete dissolution of the substance.

***Related substances***: TLC replaced by HPLC in accordance with current policy.
**Impurities**: transparency list dividing the impurities into specified and other detectable impurities introduced.

## Oxygen (98 per cent) (3098)

Before publication of this monograph, the Ph. Eur. included two monographs for oxygen:

- *Oxygen (0417)*

When this monograph was initially drafted in the late sixties, there were several viable manufacturing methods considered that could be used to produce oxygen for medicinal use with a nominal content greater than 99.0 per cent. When the monograph was subsequently revised in 1997, it was found that cryogenic distillation of ambient air was the most common method used to produce this grade of oxygen for use in healthcare facilities. To reflect the production capabilities of cryogenic distillation plants, the minimum nominal content was also increased to 99.5 per cent *V/V* oxygen.

- *Oxygen (93 per cent) (2455)*

This monograph was first published in the Ph. Eur. in 2010 to cover oxygen produced on healthcare facility sites using a single-stage adsorption plant. These plants use zeolites/ molecular sieves to separate the oxygen from ambient air, producing oxygen with a nominal content between 90.0 per cent and 96.0 per cent, with the remainder being argon and nitrogen.

As these plants were already in use, the call for another monograph for oxygen was prompted primarily by the need to cover the oxygen they produced. The monograph was therefore elaborated to provide a pharmacopoeial standard that would enable healthcare facilities to control the quality of oxygen produced on-site.

Since the introduction of the Oxygen (93 per cent) monograph, advances have been made in the design of adsorption plants used to produce oxygen. One such development is the introduction of a second stage adsorption process designed to remove argon. These plants are able to produce oxygen with a nominal content of 98.0 per cent (varying between 96 and 100 per cent). The oxygen content can vary depending on plant throughput, with the remainder of the gas containing lower amounts of argon and nitrogen compared to that produced by a single-stage plant.

These developments prompted the decision to elaborate a monograph for *Oxygen (98 per cent) (3098)*.

The quality of the gas produced is controlled by the design of the plant and the specification of the materials used in the adsorption columns, based on the design throughput specified by the healthcare facility. However, the environment in which the plant is installed (and the quality of the air used to supply it) may have an adverse effect on the gas quality. To ensure that any potential impurities in the ambient air are not overlooked, the monograph requires a risk assessment to be performed to identify any potential impurities not listed in the monograph and to use the outcome to perform any necessary additional tests. As the quality of the gas produced is based on the design throughput, the risk assessment should also take account of the quality of the gas produced under maximum performance conditions.

The Tests section of the monograph prescribes a number of purity requirements. These describe a single set of quality requirements for the gas. The methods prescribed are quantitative, have been suitably validated and are considered state of the art. Compliance with the Ph. Eur. requires the performance of these tests or the demonstration that the gas would comply if tested (see General Notices). The monograph does not exclude the performance of additional tests on site using semi-quantitative methods such as indicator tubes, in the form of spot checks by the healthcare facility to verify the quality of the gas at the terminal outlet of the medical gas pipeline; such practice would be outside the scope of the Ph. Eur.

## Pentaerythrityl tetranitrate, diluted (1355)

***Definition***: chemical name updated.

***Identification***:

*- test A: in line with the revision of general method 2.2.32, the reference to diphosphorus pentoxide has been deleted;*

*- test C: modified in order to avoid the use of ethylene chloride R (REACH); TLC silica gel G plate R replaced with TLC silica gel plate R.*

***Related substances***: grades of solvents amended in accordance with the Technical Guide (2022); reagent used to describe stationary phase modified.

## Reserpine (0528)

***Second identification***: tests deleted as the substance is no longer used in pharmacies.

***Identification (IR)***: preparation of the discs deleted.

## Rutoside trihydrate (1795)

The test for related substances has been updated:

- the gradient has been modified to improve the method robustness;

- quantitative expression used for the limits;

- 3 new specified impurities have been added;

- the limits have been updated or confirmed (for A, B and C).

## Sorbitol, liquid, partially dehydrated (2048)

***Assay***: column temperature and injection volume decreased to improve the resolution of the sorbitol peak.

## Sucrose (0204)

***Functionality-related characteristics***: in line with revised general chapter *2.9.34*, "*Bulk and tapped density*" has been changed to "*Bulk density of powders*".

## Tamoxifen citrate (1046)

***First identification***: test relabeled due to changes in the second identification.

***Second identification***: previous test A (by UV) deleted as it is not feasible in pharmacies; previous test C (by TLC) deleted and new test B (by TLC) with double detection introduced.

***Related substances***: grades of solvents amended in accordance with Technical Guide (2022).