# Ontwikkelingen in de Europese Farmacopee


PUOZ Labdag 22 november 2016

Oscar Smeets, KNMP - LNA

# KNMP-organisatie te Den Haag

# Laboratorium & Apotheek

# Actuele ontwikkelingen LNA producten

KNMP-kennisbank

- FNA-voorschriften met kwaliteitseisen en LNA-onderzoeksvoorschriften (nov 2016)
  - Amlodipinedrank
  - Valacicyclovirdrank
- LNA-procedures en LNA-mededelingen

Farmaceutisch analytisch ringonderzoek

Deeltjestelonderzoek voor parenteralia en oogdruppels (veldnorm in Ph. Eur?)

Specifieke analyses op contractbasis

- Voorraadbereidingen en grondstoffen controles
- Individuele bereidingen: validatie analyses
- Uiteenvaltijd zetpillen en oplossnelheid capsules/tabletten
- Stabiliteitsonderzoek

Microbio (nieuwe versie): aseptische handelingen monitoren en spiegelen

Helpdesk: jaarlijks ruim 3000 vragen, 070-3737370 of lna@knmp.nl

# Overzicht presentatie

- Farmacopees
  - Algemeen
  - Nederlandse inbreng

- Ontwikkelingen Ph. Eur.
  - Pharmeuropa/Technical Guide
  - Nieuwe monografieën
  - Nieuwe kwaliteitsdocumenten

# Farmacopee

Een farmacopee is een officieel, van staatswege uitgegeven handboek met voorschriften voor de bereiding van geneesmiddelen voor menselijk en dierlijk gebruik, en de vereisten waaraan zij moeten voldoen.

# Besluit Geneesmiddelenwet

Artikel 2
Geneesmiddelen die in een apotheek zijn bereid, niet zijnde geneesmiddelen voor onderzoek, worden slechts ter hand gesteld indien zij voldoen aan de voorschriften van de Europese Farmacopee of, bij ontstentenis daarvan, aan een in een lidstaat officieel in gebruik zijnde farmacopee, dan wel, bij ontstentenis daarvan, aan een in de Verenigde Staten of Japan officieel in gebruik zijnde farmacopee. Voor de samenstelling worden deugdelijke bestanddelen gebruikt.

# Belangrijkste Farmacopees

- Europees Farmacopee: sinds 1964 (Ph. Eur)
- Nederlandse Farmacopee opgeheven in 1993
- Britse Farmacopee (BP)
- Duitse Farmacopee (DAB)
- Franse Farmacopee: zie http://ansm.sante.fr/Mediatheque/Publications
- Zwitserse Farmacopee (Helv)
- Portugese Farmacopee (Por)
- Amerikaanse Farmacopee (USP)
- Japanse Farmacopee (Jpn)

**Publications**

> Informations récentes

**Rapports/Synthèses**

**Bulletins / dépliants**

**Formulaires et démarches**

**Interventions publiques**

**Ordres du jour/comptes rendus des commissions/comités/groupes de travail**

**Listes et répertoires**

**Pharmacopée française**

> Plan / Préambule /index
> Textes généraux
> Méthodes analytiques
> Matériaux / Récipients
> Réactifs
> Formes pharmaceutiques
> Immunosérum
> Substances d'origine végétale
> Préparations homéopathiques - Français
> Préparations homéopathiques - Anglais

## Substances d'origine chimique

Liste des monographies françaises des substances d'origine chimique

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

### A

- Amprolium (chlorhydrate d') pour usage veterinaire (1986) (14/02/2012) (241 ko)

### B

- Benzododécinium (bromure de) (1996) (14/02/2012) (260 ko)
- Bismuth (sous-succinate de) (1991) (14/02/2012) (235 ko)
- Bleu patenté V (1990) (14/02/2012) (263 ko)
- Boldine (1995) (14/02/2012) (278 ko)

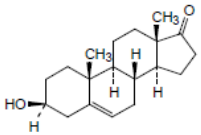
### C

- Calcium (hydroxyde de) (solution d') (2007) (14/02/2012) (234 ko)
- Calcium (oxyde de) (2007) (14/02/2012) (234 ko)

# PRASTÉRONE

**Prasteronum**

*La dénomination usuelle de la Prastérone est : DHEA (déhydroépiandrostérone).*




$C_{19}H_{28}O_2$ $M_r$ 288,4

## DÉFINITION

3β-hydroxyandrost-5-én-17-one.

*Teneur* : 97,5 pour cent à 102,0 pour cent (substance anhydre et exempte de solvants).

## PRODUCTION

Dans les cas appropriés, la prastérone est conforme à la monographie Produits comportant un risque de transmission d'agents d'encéphalopathies spongiformes animales (1483).

## CARACTÈRES

*Aspect* : poudre fine, cristalline, blanche ou sensiblement blanche.

*Solubilité* : pratiquement insoluble dans l'eau, facilement soluble dans l'éthanol à 96 pour cent et dans le chlorure de méthylène.

La prastérone présente le phénomène du polymorphisme (*5.9*).

## IDENTIFICATION

*Première identification* : B.

*Seconde identification* : A, C.

A. Point de fusion *(2.2.14)* : 146 °C à 151 °C.

B. Spectrophotométrie d'absorption dans l'infrarouge *(2.2.24)*.

*Comparaison* : *prastérone SCR fr.*

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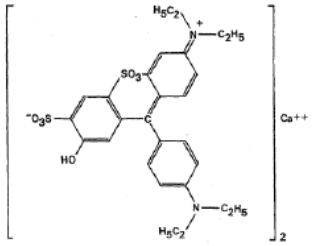
*Les prescriptions générales et les monographies générales de la Pharmacopée européenne ainsi que le préambule de la Pharmacopée française s'appliquent.*

# BLEU PATENTÉ V

## Caeruleum protectum V



$C_{54}H_{62}CaN_4O_{14}S_4$ $M_r$ 1159

DÉFINITION

Bis[[[(diéthylamino)-4-phényl][(diéthyliminio)-4-cyclohexadiène-2,5-ylidène]méthyl]-4-hydroxy-6-benzènedisulfonate-1,3] de calcium.

*Teneur* : au minimum 85,0 pour cent (substance desséchée).

CARACTÈRES

*Aspect* : poudre bleu foncé.

*Solubilité* : assez soluble dans l'eau, peu soluble dans l'éthanol anhydre, très peu soluble à pratiquement insoluble dans l'acétone et pratiquement insoluble dans le chlorure de méthylène.

La solution à 1 g/L est verte à pH 2,5 et bleu-vert à pH 7.

IDENTIFICATION

A. Spectrophotométrie d'absorption dans l'ultraviolet et le visible (*2.2.25*).

*Solution à examiner* (a) : Prélevez 1 mL de la solution S (voir Essai) et complétez à 100 mL avec de l'*acide chlorhydrique 0,1 M*.

*Solution à examiner* (b) : Prélevez 1 mL de la solution S et complétez à 200 mL avec de l'*hydroxyde de sodium 0,1 M*.

*Région spectrale* : 230-650 nm pour la solution à examiner (a) ; 230-650 nm pour la solution à examiner (b).

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*Les prescriptions générales et les monographies générales de la Pharmacopée européenne ainsi que le préambule de la Pharmacopée française s'appliquent.*

# Ph. Eur. 9th Edition

## Earliest access to all European quality standards that come into effect on 1 January 2017

The European Pharmacopoeia (Ph. Eur.) is Europe's legal and scientific benchmark for pharmacopoeial standards which contribute to delivering high quality medicines in Europe and beyond.


The Ph. Eur. is applicable in 37 European countries and used in over 100 countries worldwide.

It delivers crucial information earlier than any other pharmacopoeia – the 9th Edition will be released in mid-2016.

With 121 new and 1,403 revised texts, over 50% of the 9th Edition's content is new compared to the 8th Edition.

For more information about the European Pharmacopoeia, go to our European Pharmacopoeia section

## Versions and Subscriptions

The Ph. Eur. is supplied in a variety of formats:

- **Book Version:** Available in English or French. The 9th Edition will consist of 3 initial volumes (9.0) and 8 non-cumulative supplements (9.1 to 9.8). Volumes 1, 2 and 3 combined contain 2329 monographs (including dosage forms), 358 general texts (including general monographs and methods of analysis) and around 2600 descriptions of reagents. New feature: it includes a direct link to the KNOWLEDGE database from each monograph. Free access to online archives. Download the 9.0 Index and the 9.0 List of contents
- **Online Version:** Completely cumulative, tablet and smartphone friendly. Bilingual: English and French. Changes (inserted or deleted texts) indicated in both html and pdf versions. Possibility of adding RSS feeds for specific queries. Direct access to the KNOWLEDGE database, with a powerful search engine. Read the Technical Specifications
- **USB Version:** Completely cumulative and bilingual (English and French). Allows easy access to the Ph. Eur. while on the move or in environments where the use of the book or online versions would be inappropriate or impractical. It is also ideal for users who have more than one computer. The 2017 subscription will consist of three USB keys (9.0, 9.1 and 9.2). As from 2017 (i.e. from 9.3), the USB format will be replaced by a downloadable version. Read the Technical Specifications
- **Languages**: The book version is available in English and


## Video

The 9th Edition European Pharmacopoeia: Maintaining high quality standards in a dynamic global environment

## Publication Schedule 9th edition

**(Book, Online and USB Stick)**

# Revision of guideline for use of a CEP in another CEP application

Back

CERTIFICATION OF SUITABILITY (CEP) PROCEDURE OF CERTIFICATION (GENERAL) | NEWS | 26 SEPTEMBER 2016 | STRASBOURG, FRANCE

EDQM has revised the policy regarding the use of a CEP to describe a material in an application for another CEP. The policy is described in the revised document, Use of a CEP to describe a material in an application for another CEP (PA/PH/CEP (14) 06 1R, September 2016).

- Use of a CEP to describe a material used in an application for another CEP

The policy has been revised to clarify the requirements and to reflect the fact that such materials may be either intermediates or starting materials in the new CEP application.



AGENDA

17 OCTOBER 2016
STRASBOURG, FRANCE
The Chinese and European Pharmacopoeias – The new editions

03 NOVEMBER 2016 TO 04 NOVEMBER 2016
WASHINGTON, USA
12th Annual International Symposium on Pharmaceutical Ref...

08 NOVEMBER 2016 TO 09 NOVEMBER 2016
STRASBOURG, FRANCE
EU Batch Release for Human Vaccines: A Practical Overview...

See all events »

# European Pharmacopoeia:
## 9th edition and its Supplements Publication schedule

| Commission Sessions | | Edition/ Supplement | Publication schedule | Corrections to be taken into account as soon as possible and not later than | Implementation date |
|---|---|---|---|---|---|
| Session No. | Date | | | | |
| **153** | **November 2015** | **9th Edition** | **July 2016** | **31 August 2016** | **1 January 2017** |
| 154 | March 2016 | 9.1 | October 2016 | 30 November 2016 | 1 April 2017 |
| 155 | June 2016 | 9.2 | January 2017 | 28 February 2017 | 1 July 2017 |
| 156 | November 2016 | 9.3 | July 2017 | 31 August 2017 | 1 January 2018 |
| 157 | March 2017 | 9.4 | October 2017 | 30 November 2017 | 1 April 2018 |
| 158 | June 2017 | 9.5 | January 2018 | 28 February 2018 | 1 July 2018 |
| 159 | November 2017 | 9.6 | July 2018 | 31 August 2018 | 1 January 2019 |
| 160 | March 2018 | 9.7 | October 2018 | 30 November 2018 | 1 April 2019 |
| 161 | June 2018 | 9.8 | January 2019 | 28 February 2019 | 1 July 2019 |
| **162** | **November 2018** | **10th Edition** | **July 2019** | **31 August 2019** | **1 January 2020** |

# Ph. Eur. en Nederland (1)

- NL is een van de 37 lidstaten
- EDQM: European Directorate for the Quality of Medicines & Healthcare in Straatsburg
- 3x per jaar Ph. Eur. Commissie vergadering
- NFA: Nederlandse Farmacopee Autoriteit
- Inbreng via Nederlandse Delegatie
- Secretaris NL Delegatie Ellen Lamme, RIVM
- Actviteiten NL delegatie  http://www.rivm.nl/ph-eur

**In dit onderwerp**

**Europese Farmacopee**
+ Wat is de Europese Farmacopee
+ Nederlandse bijdrage aan de Europese Farmacopee
+ Vergaderingen en nieuws
› Rapport "Europese Farmacopee. Gouden standaard bij de bereiding van geneesmiddelen"
› Contact

**Documenten en Publicaties**
+ **Rapporten**

# Europese Farmacopee

**Op deze en de onderliggende pagina's vindt u informatie over de Europese Farmacopee, met name de ontwikkelingen die plaatsvinden en de beslissingen die genomen zijn.**
**Deze informatie is afkomstig van de Nederlandse delegatie van de Europese Farmacopee Commissie (EFC) en is voor iedereen die hierin geïnteresseerd is, in het bijzonder voor de farmaceutische industrie en (ziekenhuis)apotheken.**

Het RIVM voert het secretariaat van de Nederlandse Farmacopee Autoriteit in opdracht van de minister van VWS.

Dit onderwerp is gemaakt in opdracht van de Inspectie Gezondheidszorg.

Delen op:

**Andere informatiebronnen**
› European Pharmacopeia 8th edition
› Pharmeuropa bio and scientific notes

**Downloads**
› Besluitenlijst EFC-vergadering 139
10 februari 2014, PDF | 249kB
› Besluitenlijst EFC-vergadering 140
10 februari 2014, PDF | 198kB
› Besluitenlijst EFC-vergadering 141
10 februari 2014, PDF | 219kB
› Besluitenlijst EFC-vergadering 142
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› Besluitenlijst EFC-vergadering 143
21 februari 2013, PDF | 207kB
› Besluitenlijst EFC-vergadering 144
21 februari 2013, PDF | 239kB
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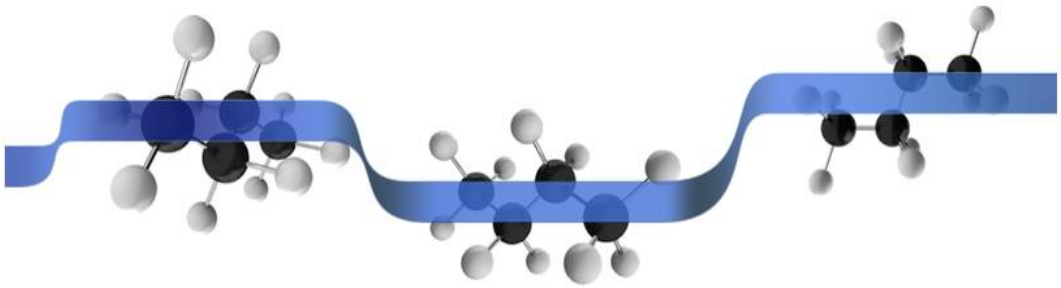
08 mei 2013, PDF | 171kB
› Besluitenlijst EFC-vergadering 146
10 februari 2014, PDF | 226kB
› Besluitenlijst EFC-vergadering 147
10 februari 2014, PDF | 261kB
› Besluitenlijst EFC-vergadering 148
26 november 2014, PDF | 118kB
› Besluitenlijst EFC-vergadering 149
26 november 2014, PDF | 123kB

# Ph. Eur. en Nederland (2)

- Ontwerpen en revisies van monografieen door:
  - 22 NL experts in 18/20 groepen
  - 19 NL specialisten in 22/51 groepen
  - Vergaderen 2-3 keer per jaar in Straatsburg
  - EDQM ondersteund
- Nederlandse Werkgroep Monografie Evaluatie: levert input voor commentaar op nieuwe monografieen of revisies
- Probleem is labcapaciteit: kwaliteit monografie daardoor niet altijd optimaal

# Pharmeuropa, Pharmeuropa Bio & Scientific Notes



Pharmeuropa is a free online EDQM publication providing:

- public inquiries on draft European texts or on matters of general policy,
- the latest official announcements on freshly adopted monographs,
- the latest news on Pharmacopoeial harmonisation,
- a readers' tribune and

## Online Access

Search Pharmeuropa

It is necessary to register in order to have full access to the content of Pharmeuropa online.

How to register: Instructions

## ICH Guideline on Residual Solvents (1997)

A special issue of Pharmeuropa is dedicated to toxicology and the scientific basis for limits for residual solvents.

ICH Guideline on Residual Solvents

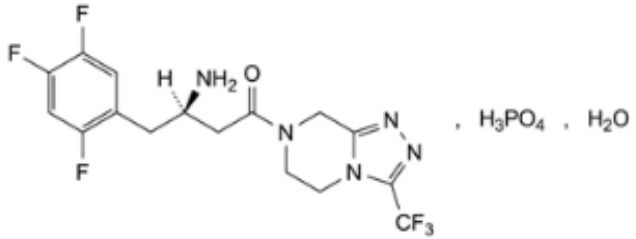
## Catalogue

# Specifieke Product monografieen

- 1999 Discussie op agenda
- 2000 Geen groen licht door Commissie
- 2011 Reflection paper: toch niet doen?
- 2012 Groen licht voor pilot
- 2014 Resultaat twee concepten
- 2016 Sitagliptine Phosphate monohydrate tablets

# SITAGLIPTIN PHOSPHATE MONOHYDRATE TABLETS

## Sitagliptini phosphatis monohydrici compressi




$C_{16}H_{18}F_6N_5O_5P,H_2O$ $M_r$ 523.3

DEFINITION

(3*R*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate monohydrate.

Sitagliptin phosphate monohydrate tablets contain *Sitagliptin phosphate monohydrate (2778)*.

*The tablets comply with the monograph Tablets (0478) and with the following additional requirements*.

*Content*: 95.0 per cent to 105.0 per cent of the content of sitagliptin ($C_{16}H_{15}F_6N_5O$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay with a diode array detector.

*Spectral range*: 200-350 nm.

**Dissolution** (*2.9.3, Apparatus 2*).

*Dissolution medium*: *0.01 M hydrochloric acid*; use 1 L for the test.

*Rotation speed*: 50 r/min.

*Time*: 30 min.

*Analysis*

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

*Reference solution.* Dissolve a suitable quantity of *sitagliptin phosphate monohydrate CRS* in a suitable quantity of the dissolution medium to obtain a concentration of sitagliptin corresponding to the theoretical concentration of sitagliptin in the test solution, based on the labelled content of the tablets.

*Detection*: spectrophotometer at 266 nm.

*Injection*: test solution from the dissolution test(62) and reference solution.

*Run time*: twice the retention time of sitagliptin.

Calculate the percentage dissolved of sitagliptin ($C_{16}H_{15}F_6N_5O$) taking into account the assigned content of *sitagliptin phosphate monohydrate CRS*.

*Acceptance criteria*:

– an evaluation is carried out according to Table 2.9.3.-1, with Q = 75 per cent.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

*Injection*: test solution and reference solution (a).

*Run time*: twice the retention time of sitagliptin.

*System suitability*: reference solution (a):

– *repeatability*: maximum relative standard deviation of 1.5 per cent for the peak due to sitagliptin after 6 injections.

Calculate the percentage content of sitagliptin ($C_{16}H_{15}F_6N_5O$) taking into account the assigned content of *sitagliptin phosphate monohydrate CRS*.

# Beleid specifieke Product monografieen

- Concurrentie met BP en USP
- Vanwege juridische redenen alleen grondstoffen op einde patent
- Producten van single naar multiple source
- Dagelijkse praktijk:
  - alleen voorbeeld in algemene zin
  - voorlopig geen bruikbare monografieen

# Water for injections

- Supplement 9.1: Aangepaste monografie
- Productietechniek: Reversed Osmose is toegestaan
- Reden: nieuwe dialysetechniek: o.a. Haemodialyse
- Nederland heeft grote bijdrage geleverd
- UMCG: Prof. D.J. Touw

# WATER FOR INJECTIONS

## Aqua ad iniectabile

$H_2O$ $M_r$ 18.0

DEFINITION

Water for the preparation of medicines for parenteral administration when water is used as vehicle (water for injections in bulk) and for dissolving or diluting substances or preparations for parenteral administration (sterilised water for injections).

## Water for injections in bulk

PRODUCTION

Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water. It is produced either:

- by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets; or
- by a purification process that is equivalent to distillation. Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration, is suitable. Notice is given to the supervisory authority of the manufacturer before implementation.

For all methods of production, correct operation monitoring and maintenance of the system are essential. In order to ensure the appropriate quality of the water, validated procedures, in-process monitoring of the electrical conductivity, and regular monitoring of total organic carbon and microbial contamination are applied.

The first portion of water obtained when the system begins to function is discarded.

# Water

**Water for injections (0169)**
***Production***: revision to include purification processes equivalent to distillation (such as reverse osmosis coupled with appropriate techniques) for producing water for injections (WFI), in addition to distillation; use of non-distillation technologies for the production of WFI requires that notice is given to the supervisory authority of the manufacturer before implementation.

The revision of the monograph is supported by the evidence provided in the document ‘Reverse osmosis in Ph. Eur. monograph *Water for injections (0169)*’, published in the Knowledge database under ‘Additional information’.

# Beleid monoklonale antilichamen

- Algemene monografie nummer 2031
- Eerste stof: Infliximab nummer 2928
- Intentie: andere mabjes gaan volgen

# MONOCLONAL ANTIBODIES FOR HUMAN USE

## Anticorpora monoclonalia ad usum humanum



### DEFINITION

Monoclonal antibodies for human use are preparations of an immunoglobulin or a fragment of an immunoglobulin, for example, F(ab')2, with defined specificity, produced by a single clone of cells. They may be conjugated to other substances, including for radiolabelling.

They can be obtained from immortalised B lymphocytes that are cloned and expanded as continuous cell lines or from rDNA-engineered cell lines.

Examined under suitable conditions of visibility, they are practically free from particles.

Currently available rDNA-engineered antibodies include the following antibodies.

*Chimeric monoclonal antibodies*: the variable heavy- and light-chain domains of a human antibody are replaced by those of a non-human species that possess the desired antigen specificity.

*Humanised monoclonal antibodies*: the 3 short hypervariable sequences (the complementarity-determining regions) of non-human variable domains for each chain are engineered into the variable domain framework of a human antibody; other sequence changes may be made to improve antigen binding.

*Recombinant human monoclonal antibodies*: the variable heavy- and light-chain domains of a human antibody are combined with the constant region of a human antibody.

Monoclonal antibodies obtained from cell lines modified by recombinant DNA technology also comply with the requirements of the monograph *Products of recombinant DNA technology (0784)*.

This monograph applies to monoclonal antibodies, including conjugates, for therapeutic and prophylactic use and for use as *in vivo* diagnostics. It does not apply to monoclonal antibodies used as reagents in the manufacture of medicinal products. Nor does it apply to monoclonal antibodies produced in ascites, for which requirements are decided by the competent authority.

### PRODUCTION

*GENERAL PROVISIONS*

Production is based on a seed-lot system using a master cell

**Reference:** PA/PH/Exp. MAB/T (16) 5 ANP 1

*NOTE ON THE MONOGRAPH* 2

*The European Pharmacopoeia (Ph. Eur.) Commission is presently conducting a pilot phase on the development of Ph. Eur. texts for monoclonal antibodies using infliximab as a case study (multi-source approach).* 3

*Based on extensive laboratory work and conclusive experimental data generated in the collaborative study for infliximab method verification, a monograph for Infliximab concentrated solution is now ready for public consultation. This monograph proposal is the result of a collaborative effort of a large number of laboratories and of a careful assessment of the process dependent product heterogeneity (e.g. glycosylation, charged variants etc.).* 4

*In order to further decide on the adequacy and usefulness of such a monograph, the Ph. Eur. Commission agreed to publish the draft text in Pharmeuropa to collect comments from users. A decision on the adoption of the final text for publication in the Ph. Eur. will be taken based on the outcome of the public enquiry, thereby helping to progress the pilot phase.* 5

***Definition**: it is to be noted that the potency is expressed in International Units (IU), which are currently being defined by the World Health Organisation (WHO). The potency range indicated in the current draft will have to be confirmed once the first International Standard for Infliximab with an assigned in vitro bioactivity expressed in IU is established (Note: the establishment study takes place simultaneously with the monograph elaboration).* 6

***Production**: due to their complexity and the link between drug substance quality and the manufacturing process, tests that measure process dependent heterogeneity are mainly seen as a demonstration of production consistency. These tests cannot be included in the Tests section of the monograph as a direct transfer of the lot-release specifications set. As a result, the glycan analysis and charged variants determination are included in the Production section of the monograph in accordance with the provisions given in the Ph. Eur. General Notices, as these tests cannot be performed by an independent analyst for the following reasons:* 7

- *the glycan profile and charge heterogeneity depend on the manufacturing process;* 8
- *the tests prescribe the use of an in-house reference preparation and this material is available only to the manufacturer;* 9
- *the user needs acceptance criteria in the form of numerical limits, which are not prescribed in the monograph; given the variability of the glycan profile and the heterogeneity of the charged variants associated with process changes, acceptance criteria in the form of "one-fits-all" numerical limits for specific glycan species and charged isoforms may not be suitable and have to be set by the manufacturer in agreement with the competent authority.* 10

**XXXX:2928** 11

# INFLIXIMAB CONCENTRATED SOLUTION 12

## Infliximabum solutio concentrata 13

heavy chain

```
EVKLEESGGG  LVQPGGSMKL  SCVASGFIFS  NHWMNWVRQS   40
PEKGLEWVAE  IRSKSINSAT  HYAESVKGRF  TISRDDSKSA   80
VYLQMTDLRT  EDTGVYYCSR  NYYGSTYDYW  GQGTTLTVSS  120
ASTKGPSVFP  LAPSSKSTSG  GTAALGCLVK  DYFPEPVTVS  160
```

# Zware metalen

- Per editie 9 algemene test niet meer opgenomen bij stoffen voor humane toepassing
- Slechte reproduceerbaarheid
- Basis hiervan ICH Q3D guideline: per januari 2018 van kracht
- Nu elementen specifiek bepalen met AAS

04/2017:20214

# 2.2.14. MELTING POINT - CAPILLARY METHOD

The melting point determined by the capillary method is the temperature at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase (i.e. clear point). The melting point determined by this method is specific to the methodology (e.g. heating rate) described in this chapter. Similarly, whenever the use of certified reference materials is required, their certified values refer to the described analytical procedure.

When prescribed in the monograph, the same apparatus and method are used for the determination of other factors, such as meniscus formation or melting range, that characterise the melting behaviour of a substance.

*Equipment.* The equipment consists of a metal heating block with 1 or more compartments for capillary tubes, or of a suitable glass vessel containing a liquid bath (e.g. water, liquid paraffin or silicone oil) and fitted with a suitable means of heating and stirring. The equipment is equipped with a temperature sensor or a suitable certified thermometer allowing readings at least to the nearest 0.1 °C.

Samples are introduced into the equipment in glass capillary tubes. The dimensions are chosen according to the manufacturer's requirements, typically with an external diameter of 1.3-1.5 mm and a wall thickness of 0.1-0.3 mm. In some equipment glass slides are used instead of capillary tubes.

The equipment is capable of heating samples at a rate of 1 °C/min or less. The accuracy of the equipment is at most ± 0.5 °C.

Detection can be performed either visually or instrumentally. In the case of instrumental detection, this is generally performed by image recording and subsequent analysis or by a photodetector that measures the transmitted or reflected light from the sample.

*Method.* The substance is previously treated as described in the monograph. Coarse crystals are to be avoided as they might lead to false results. If necessary, samples are crushed into a fine powder. Unless otherwise prescribed, dry the finely powdered substance *in vacuo* over *anhydrous silica gel R* for 24 h. Introduce a sufficient quantity into a capillary tube to give a compact column as described by the instrument manufacturer (e.g. 4-6 mm in height). Raise the temperature of the apparatus to about 5 °C below the presumed melting point. Allow the temperature to stabilise and then introduce the capillary tube into the instrument. Finally, adjust the rate of heating to about 1 °C/min unless otherwise prescribed.

In the case of instrumental detection, follow the instrument manufacturer's requirements for the determination of the melting point. For visual detection, record the temperature at which the last particle of the substance to be examined passes into the liquid phase.

Samples can be measured in parallel if the instrument allows multiple sample processing.

*System suitability.* Carry out a system suitability test before the measurements for example by choosing a suitable reference material with a melting point close to that expected for the substance to be examined.

*Qualification / Calibration of the equipment.* The qualification / calibration is carried out periodically according to the instrument manufacturer's requirements, using at least 2 certified reference materials. These are selected to cover the temperature range that is used on the equipment. Use capillary tubes with the same dimensions as those used for sample measurement.

Guidance on how to compare results obtained from certified reference materials with values from the certificates can be found on the European Reference Materials (ERM) website (Application note 1).

# Smeltpuntsbepaling

***System suitability.*** Carry out a system suitability test before the measurements for example by choosing a suitable reference material with a melting point close to that expected for the substance to be examined

Voorbeelden:

- Vanilline 83 ºC
- Sulfanilamide 166 ºC
- Sulfapyridine 193 ºC
- Coffeïne 237 ºC

Technical guide for the

# ELABORATION OF MONOGRAPHS

European Pharmacopoeia

EDQM
7th Edition
2015

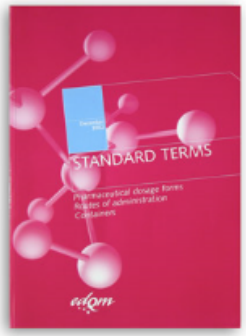
# Kwaliteit acetonitril en methanol

| **Wavelength intervals** | **Acetonitrile grade** | **Methanol grade** |
|---|---|---|
| λ ≥ 250 nm | *Acetonitrile R* | *Methanol R* |
| 220 nm ≥ λ < 250 nm | *Acetonitrile for chromatography R* | *Methanol R1* |
| λ < 220 nm | *Acetonitrile R1* | *Methanol R2* |

# En verder……

- Kinderformularium
  - Nederlandse inbreng door dr. L. Hanff, ErasmusMC
  - NL input via FNA voorschriften
  - Nu bezig met inventarisatie en selectie producten
- Standard terms
  - Nederland en Belgie gaan inhaalslag maken
  - Niet alleen vertaling van geregistreerde toedieningsvormen maar nu ook de overige

# Standard Terms Database




The lists of Standard Terms were initially drawn up in response to a request from the European Commission, and cover pharmaceutical dose forms (also known as dosage forms), routes and/or methods of administration, and containers, closures and delivery devices, for medicines both for human and for veterinary use. The database also contains combinations of terms, for example to describe where two or more items are packaged together, or where a pharmaceutical dose form and a container are described using a single term. Also listed are patient-friendly terms, which are generally shorter terms that, where justified and authorised by the competent authority, may be used on certain labels where space is limited.

The Standard Terms database gives the **equivalents of several hundred terms in 33 world languages**: Albanian, Bosnian, Bulgarian, Chinese, Croatian, Czech, Danish, Dutch, English, Estonian, Finnish, French, German, Greek, Hungarian, Icelandic, Italian, Kazakh, Latvian, Lithuanian, Macedonian, Maltese, Norwegian, Polish, Portuguese, Romanian, Serbian, Slovak, Slovene, Spanish, Swedish, Turkish and Ukrainian.
Standard Terms are used in European Marketing Authorisation applications, the Summary of Product Characteristics (SmPC), labelling and electronic communications.

The database also provides a summary of changes made to the lists on given dates, recent decisions taken by the Standard Terms Working Party and the European Pharmacopoeia Commission, and an explanation of the different statuses of the terms.

Further information is available in the Introduction and guidance for use, which explains the structure of the database and details the **general principles and instructions for use of the lists of terms.** The Change request form is used **for requesting additions and modifications**; please note that the submission of requests to the EDQM is restricted to national European licensing or pharmacopoeia authorities, the EMA and the EU Commission. Links to both of these documents are provided within the database.

Standard Terms was originally a printed publication, until the 5th edition, which was published in December 2004 alongside an online database. Since April 2008, Standard Terms has only been available as an online database. In November 2014, a major new update was introduced with the development of the current database, and access was made available free of charge for all users after registration with the EDQM Publications registration website

## Search online:

Search Standard Terms

Accessible free of charge to all customers who request access via their Register account

## How to request access to Standard Terms

Customers must first have an account with the EDQM Publications registration website from which the option to access the free Standard Terms Online database can be selected under the 'Free access' item in the menu.

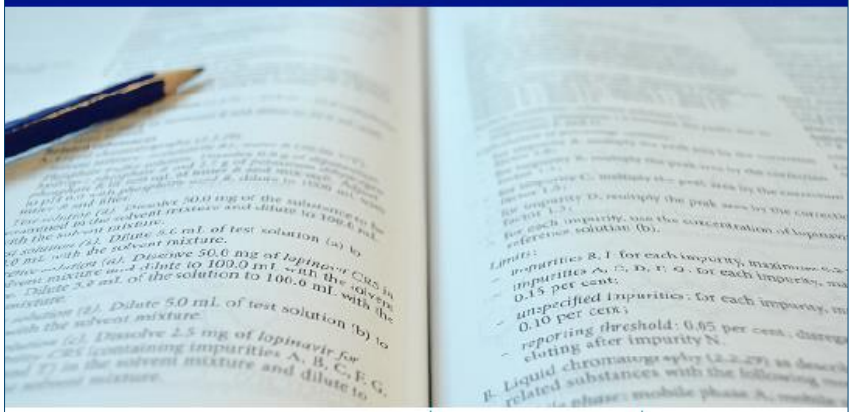
- Go to the EDQM Registration website

## Overview Products & Services

2016 Products & Services

# Style Guide of the European Pharmacopoeia

# Guide de rédaction de la Pharmacopée Européenne



European Pharmacopoeia
Pharmacopée Européenne

August 2014
Août 2014

edqm
European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

KNMP

# Changes in titles for the 9th Edition

Following the implementation of the new policy for hydrates (see Style guide 2014, page 19), the word 'anhydrous' will be deleted from the titles of the monographs listed in the table below. These changes in title will be implemented for the 9th Edition and will therefore come into force on **1 January 2017**.

| Old title | New title | Number |
|---|---|---|
| Ampicillin, anhydrous | **Ampicillin** | 0167 |
| Beclometasone dipropionate, anhydrous | **Beclometasone dipropionate** | 0654 |
| Calcipotriol, anhydrous | **Calcipotriol** | 2011 |
| Calcium acetate, anhydrous | **Calcium acetate** | 2128 |
| Calcium hydrogen phosphate, anhydrous | **Calcium hydrogen phosphate** | 0981 |
| Calcium lactate, anhydrous | **Calcium lactate** | 2118 |
| Chlorobutanol, anhydrous | **Chlorobutanol** | 0382 |
| Citric acid, anhydrous | **Citric acid** | 0455 |
| Copper sulfate, anhydrous | **Copper sulfate** | 0893 |
| Disodium phosphate, anhydrous | **Disodium phosphate** | 1509 |
| Docetaxel, anhydrous | **Docetaxel** | 2593 |
| Ephedrine, anhydrous | **Ephedrine** | 0488 |
| Glucose, anhydrous | **Glucose** | 0177 |
| Lactose, anhydrous | **Lactose** | 1061 |
| Lufenuron (anhydrous) for veterinary use | **Lufenuron for veterinary use** | 2177 |
| Magnesium citrate, anhydrous | **Magnesium citrate** | 2339 |
| Nevirapine, anhydrous | **Nevirapine** | 2255 |
| Niclosamide, anhydrous | **Niclosamide** | 0679 |
| Paroxetine hydrochloride, anhydrous | **Paroxetine hydrochloride** | 2283 |
| Phloroglucinol, anhydrous | **Phloroglucinol** | 2301 |
| Sodium carbonate, anhydrous | **Sodium carbonate** | 0773 |

# De graad van hydratatie

- Monografie: kopjes titel en definitie
- Goed gedefinieerd: mono-, di-, tri-, etc hydrate
- Watervrij: anhydrous wordt niet meer gebruikt, op enkele uitzonderingen na, bv. Ethanol anhydrous
- Variabele hoeveelheid water: x-hydrate

# Quality Management (QM) Documents

Quality Management (QM) documents have been developed for application within the General European OMCL Network. They are available to download below.

Those marked with an asterisk* have been approved by the European co-operation for Accreditation (EA).

## Introduction

- Preface and Notes for Use of OMCL Quality Management Documents

## Guidelines

### Important Information

For information about the Quality Management (QM) Programme, visit the Control of Medicines section.

### Overview Products & Services

2016 Products & Services

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## Introduction

- Preface and Notes for Use of OMCL Quality Management Documents

## Guidelines

- Sub-Contracting of Tests
- Sub-Contracting of Tests Annex I: Sub-Contractor Qualification
- Sub-Contracting of Tests Annex 2: OMCL Model Contract for Sub-Contracting
- Validation of Analytical Procedures*
- Uncertainty of Measurement-Part 1: General OMCL Policy for implementation of Measurement of Uncertainty in Compliance Testing*
- Uncertainty of Measurement-Part 2: OMCL Policy on the Estimation and Application of Uncertainty in Analytical Measurement
- Evaluation & Reporting of Results – Core Document
- Evaluation & Reporting of Results – Annex 1A: Model Template for Failure Investigation of OOS Results
- Evaluation & Reporting of Results – Annex 1B: Responsibilities of the Laboratory Supervisor
- ng of Results – Annex 2A: Examples of Re-Test Programmes for Quantitative Tests

## Important Information

For information about the Quality Management (QM) Programme, visit the Control of Medicines section.

## Overview Products & Services

2016 Products & Services

# Quality Management (QM) Documents

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## Recommendation documents

- Qualification of Analytical Columns
- Qualification and Requalification of Analysts
- General Requirements for Infrequently performed techniques
- Management of Volumetric Glassware
- Interpretation of Screening Results for Unknown Peptides and Proteins by MS Based Methods

## Other documents

- Standard 'Aide-Mémoire' for the Mutual Joint Audit of Official Medicines Control Laboratories*
- 'Aide-Mémoire' for Environmental Conditions & Treatment of Biological Models*
- VBRN/ OCABR: 3R Issues for method validation and maintenance of competence

### Important Information

For information about the Quality Management (QM) Programme, visit the Control of Medicines section.

### Overview Products & Services

2016 Products & Services

# OMCL Network of the Council of Europe
# QUALITY MANAGEMENT DOCUMENT

## PA/PH/OMCL (15) 16 3R

## MANAGEMENT OF VOLUMETRIC GLASSWARE

| | |
|---|---|
| **Full document title and reference** | Management of Volumetric Glassware<br>PA/PH/OMCL (15) 16 3R |
| **Document type** | Recommendation Document |
| **Legislative basis** | |
| **Date of first adoption** | 8 January 2016 |
| **Date of original entry into force** | 15 January 2016 |
| **Date of entry into force of revised document** | |
| **Previous titles/other references / last valid version** | |
| **Custodian Organisation** | The present document was elaborated by the OMCL Network / EDQM of the Council of Europe |
| **Concerned Network** | GEON |

ANNEX 2

**Example of validation of a cleaning procedure for volumetric glassware using a glassware washing machine (source: CY – Workshop for auditors October 2015)**

1. The procedure can be used during the IQ-OQ of the new glassware washing machine and for PQ (e.g. every 6 months);
2. The laboratory chooses an available "difficult to clean" API;
3. From the volumetric flasks described in the testing method of the selected API, two of the lower and two of the maximum nominal volume flasks are selected (e.g. 2 x 5ml and 2 x 100ml volumetric flasks);
4. A reference solution of the API is prepared as described in the testing method;
5. Each of the selected volumetric flasks is filled to about 10% of its nominal volume with this reference solution, closed and shaken so the inner walls of the flasks will be covered by the liquid. They are emptied and allowed to dry;
6. The 4 flasks are then washed alone in the washing machine using the defined washing instructions (Empty Load);
7. The same procedure is performed with the maximum number of volumetric flasks that can be washed in the washing machine (Full Load);
8. All the flasks are filled with the solvent solution used for the preparation of the Reference Standard Solution and analysed with the HPLC testing method of the API used (the method is validated and the validation parameters, e.g. LOD, LOQ etc. are used);
9. No traces of the API above the LOD of the method should be detected.