# Korte kommentarer til Ph.Eur. monografier, som er ændrede i DLS 2012.1 / European Pharmacopoeia Suppl. 7.4

# Comments Concerning Revised Texts Published in Supplement 7.4

*Here follows information concerning technical modifications to revised texts adopted by the European Pharmacopoeia Commission at the March 2011 session. This information completes the modifications indicated by lines in the margin. Therefore, the information below is not necessarily exhaustive.*

## GENERAL TEXTS

### 1. General notices

*Indication of permitted limit of impurities*: paragraph modified to reflect new way of expressing acceptance criteria.

### 2.9.25. Dissolution test for medicated chewing gums

New apparatus B described.

### 2.9.40. Uniformity of dosage units

Procedure for semi-solid preparations stated; definition of *T*-value modified; definition of $\overline{w}$ modified to refer to units tested for mass variation.

### 2.9.41. Friability of granules and spheroids

Dimensions in Figure 2.9.41.-2 corrected.

### 5.2.8. Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products

This chapter is identical with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products – Revision 3 (EMA/410/01 rev. 3).

This 3rd technical revision has been undertaken to take into account advancement of science in the area of transmissible spongiform encephalopathies, as well as the evolving situation regarding Bovine Spongiform Encephalopathy (BSE) across the world.

For the classification of countries or regions according to their BSE risk, the revised chapter makes reference to the rules laid down by the World Organisation for Animal Health (OIE), replacing the previous GBR classification. Nevertheless, for countries that were classified according to the GBR criteria but not yet according to the OIE criteria, the existing GBR classification should apply, provided that there is no evidence of significant change in their BSE risk.

New criteria for the sourcing and processing of gelatin and bovine blood derivatives used in the manufacture of medicinal products for human or veterinary use have been introduced, as well as a new subsection on Peptones.

The revised Note for Guidance replaces the previous revision of the Note for Guidance (EMEA/410/01 Rev. 2 published in the Official Journal of the European Union (C 24, 28.1.2004, p. 6)) as the revised chapter replaces the last version, first published in the 5th Edition.

The revised chapter was adopted by the European Pharmacopoeia Commission on 3 May 2011, by correspondence, using the rapid implementation procedure (see Resolution AP-CPH (11) 5 of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) (Partial Agreement)). The implementation date is 1 July 2011, for both the revised chapter and note for guidance.

### 5.10. Control of impurities in substances for pharmaceutical use

*Expression of acceptance criteria*: section added to reflect new way of expressing acceptance criteria.

### 5.16. Crystallinity

*Introduction*: 'crystal classes' deleted.

## DOSAGE FORMS

### Oromucosal preparations (1807)

*Mucoadhesive preparations*: buccal films now described in this section.

*Orodispersible films*: section introduced.

### Veterinary liquid preparations for cutaneous application (1808)

Subsections Teat dips and Teat sprays amended (timing of treatment).

## HERBAL DRUGS AND HERBAL DRUG PREPARATIONS

### Equisetum stem (1825)

*Identifications A and B*: macroscopic and microscopic descriptions improved to allow better distinction between *Equisetum arvense* and other Equisetum species.

*Equisetum palustre*: *Equisetum palustre HRS* introduced to facilitate the identification of falsifications.

# MONOGRAPHS

### Amlodipine besilate (1491)

*Related substances*: methanol replaced by mobile phase in preparation of solutions to avoid any interference between impurity H and methanol; relative retentions of impurities B and G revised, based on recent data; wording for total revised in line with current policy.

### Articaine hydrochloride (1688)

*Related substances*: relative retentions of unspecified impurities deleted, in line with current policy.

### Betamethasone dipropionate (0809)

*Identification*: as IR alone is sufficient for discrimination, only IR kept in 1st identification series.

*Specific optical rotation*: dioxan replaced by less-toxic solvent.

*Related substances*: method slightly adapted to obtain better separation of impurities; limits for specified and unspecified impurities introduced; limit for total impurities lowered to 1.0 per cent.

*Assay*: UV absorbance replaced by LC from test for related substances and upper limit of content adapted accordingly.

*Impurities*: list of impurities introduced.

### Bifonazole (1395)

*Optical rotation*: test deleted.

*Related substances*: explicit acceptance criterion for unspecified impurities added, in line with general monograph *Substances for pharmaceutical use (2034)*; system suitability CRS containing all specified impurities introduced and relative retentions now given; limits updated based on available batch data.

*Impurities*: specified impurity E introduced.

### Captopril (1079)

*Related substances*: impurity J now specified; new criterion for system suitability introduced; reference solutions rearranged; total expressed in percentage only.

### Carvedilol (1745)

*Identification*: IR reference spectrum replaced by CRS, in line with current policy.

*Related substances*: specified impurity D added; CRS introduced to identify specified impurities; column size modified since currently prescribed column no longer available; system suitability criterion modified.

*Heavy metals*: test C replaced by test H to avoid ignition step.

*Impurities*: section updated in line with current policy.

### Crospovidone (0892)

Monograph revised to take account of changes resulting from international harmonisation (draft signed off by PDG in November 2010).

*Water soluble substances*: limit increased (1.5 per cent) as content of water can increase during storage.

*Assay*: method revised and harmonised with monograph *Povidone (0685)*.

### Cyproterone acetate (1094)

*Related substances*: description of reference solution (c) amended.

### Diltiazem hydrochloride (1004)

*Related substances*: introduction of relative retention and CRS for identification of specified impurity F.

*Impurities*: impurity F now listed as specified impurity.

### Diphenoxylate hydrochloride (0819)

*Characters*: melting point deleted.

*Identification A*: IR spectrum replaced by CRS in line with current policy.

*Related substances*: TLC replaced by LC.

### Ethinylestradiol (0140)

*Content*: lower limit updated.

*Related substances*: premixture of *acetonitrile R1* and *water R* now used, gradient changed accordingly.

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

### Glycerol dibehenate (1427)

*TLC identification*: resolution unsatisfactory and impossible to improve by using other solvents; TLC identification consequently replaced by cross-reference to the assay.

*Assay*: precautions are mentioned regarding the preparation and the use of the test solution; water content and glycerol content being in the same magnitude, both must be subtracted in the calculation; free fatty acids coelute with monoacylglycerols and must also be subtracted in the calculation; calculation of each glyceride content is based on the sum of the areas of the peaks due to monoacylglycerols, diacylglycerols and triacylglycerols, this is now reflected in the revised calculation formulas.

### Hydrochlorothiazide (0394)

*Content*: lower limit updated to reflect change in assay method.

*Assay*: titration replaced by LC.

### Levonorgestrel (0926)

*Specific optical rotation*: chloroform replaced by methylene chloride.

*Related substances*: TLC replaced by LC in line with current policy; limit for total impurities expressed as percentage since impurities B and U are quantified with respect to their CRSs.

*Impurities*: corresponding section updated.

### Lovastatin (1538)

*Related substances*: peak-to-valley ratio requirement modified.

### Minoxidil (0937)

*Related substances*: relative retentions and suitable CRS for system suitability and identification of specified impurities introduced; correction factor for impurity B introduced; explicit general acceptance criteria for specified and unspecified impurities introduced; disregard limit decreased, in line with general monograph *Substances for pharmaceutical use (2034)*; column changed.

*Heavy metals*: method C replaced by method H to avoid ignition step.

*Impurities*: section updated based on current information.

### Pheniramine maleate (1357)

*Definition*: limits tightened in line with Technical guide requirements for an assay by titration.

*IR identification*: sample preparation deleted in line with current policy.

*Optical rotation*: test deleted.

*Related substances*: reagent introduced for identification of impurity B; impurity A now quantified using a CRS to avoid using a correction factor; system suitability criterion changed; general acceptance criterion for unspecified impurities introduced; disregard limit decreased to 0.05 per cent in line with general monograph *Substances for pharmaceutical use (2034)*.

*Heavy metals*: method C replaced by method A to avoid ignition step.

*Assay*: sample amount decreased in line with the Technical guide.

*Impurities*: impurities C and D deleted from transparency list because considered only as theoretical impurities.

### Phenobarbital (0201)

*Related substances*: run time prolonged to ensure detection of an unspecified impurity.

### Pholcodine (0522)

*Impurities*: structure of impurity D elucidated.

### Prednicarbate (1467)

*Related substances*: explicit criterion for unspecified impurities introduced, in line with general monograph *Substances for pharmaceutical use (2034)*; relative retentions of specified impurities now given; system suitability CRS added to allow identification of specified impurities; additional system suitability criterion introduced.

### Selamectin for veterinary use (2268)

*Water*: limit widened to 'maximum 7.0 per cent' in view of batch data and the fact that the impurity profiles at both levels are similar.

### Sodium cromoglicate (0562)

*Related substances*: concentration of reference solution (b) decreased to avoid saturation of the signal for the peak due to sodium cromoglicate.

### Sodium methyl parahydroxybenzoate (1262)

### Sodium propyl parahydroxybenzoate (1263)

*Identification C*: ether replaced by a less hazardous solvent (1,1-dimethylethyl methyl ether).

### Sodium valproate (0678)

*Identification*: reference to GC method for related substances deleted, as IR and identification of sodium are sufficient for discrimination.

*Related substances*: GC method slightly modified; limits revised based on available batch data and lowered to 0.05 per cent for unspecified impurities since maximum daily dose may exceed 2 g.

*Impurities*: list updated (E, H deleted and K, L introduced) and distinction made between specified and other detectable impurities.

### Stanozolol (1568)

*Specific optical rotation*: chloroform replaced by methanol.

*Impurities A and B*: new TLC test introduced.

*Related substances*: TLC replaced by LC in line with current policy, and identification by TLC likewise replaced by LC; explicit acceptance criterion for unspecified impurities introduced.

### Talc (0438)

*Functionality-related characteristics*: text revised since talc used as anti-sticking agent.

### Testosterone propionate (0297)

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

*Identification*: IR reference spectrum replaced by CRS in line with current policy.

*Related substances*: limits updated based on available batch data; system suitability CRS introduced to allow identification of specified impurities; explicit acceptance criterion for unspecified impurities added in line with general monograph *Substances for pharmaceutical use (2034)*.

*Assay*: UV absorbance replaced by LC used in test for related substances.

*Impurities*: list updated.

### Triglycerol diisostearate (2032)

*Iodine value*: limit of 3.0 considered too low with respect to results found when analysing current production batches; limit consequently increased to 5.0. Iodine value of triglycerol diisostearate depends on fatty acid composition of the isostearic acid used as starting material.

### Valproic acid (1378)

*Identification*: 2nd identification series deleted.

*Related substances*: GC method slightly modified; limits revised based on available batch data and lowered to 0.05 per cent for unspecified impurities since maximum daily dose may exceed 2 g.

*Impurities*: list supplemented and distinction made between specified and other detectable impurities.

*Definition*: scope of the monograph extended to allow any suitable antioxidant since several antioxidants may be used by manufacturers to extend the shelf-life of wool alcohols; the suitability of the antioxidant is investigated and justified by the manufacturer; consequently, test for butylhydroxytoluene deleted.

*Melting point*: limit modified (minimum 56 °C); conditions under which the capillary tube is held after filling adjusted.

*Saponification value*: sample size increased to 10.00 g in order to increase the accuracy of the test and improve the repeatability.

*Assay*: gravimetric method replaced by a GC method which is more suitable in terms of repeatability and specificity and is derived from that described in the monograph *Cholesterol (0993)*.

*Labelling*: section deleted (see general monograph *Substances for pharmaceutical use (2034)*).

### Wool fat (0134)

*Definition*: scope of the monograph extended to allow any suitable antioxidant since several antioxidants may be used by manufacturers to extend the shelf-life of wool fat; the suitability of the antioxidant is investigated and justified by the manufacturer; consequently, test for butylhydroxytoluene deleted.

*Pesticide residues*: reagent di(2-ethylhexyl) phthalate deleted in view of its toxicity (see REACH regulation); naphthalene and sulfur deleted as it was demonstrated that they were not useful for calibration.

*Labelling*: section deleted (see general monograph *Substances for pharmaceutical use (2034)*).

*Functionality-related characteristics*: section added; drop point test moved to this section as it was not considered useful to assess the quality of the product; cross-reference to the water-absorption capacity test added.

### Wool fat, hydrogenated (0969)

*Definition*: scope of the monograph extended to allow any suitable antioxidant since several antioxidants may be used by manufacturers to extend the shelf-life of hydrogenated wool fat and to avoid the use of butylhydroxytoluene; the suitability of the antioxidant is investigated and justified by the manufacturer.

*Fatty alcohols and sterols*: pressure of carrier gas replaced by flow rate.

### Wool fat, hydrous (0135)

*Definition*: scope of the monograph extended to allow any suitable antioxidant since several antioxidants may be used by manufacturers to extend the shelf-life of hydrous wool fat; the suitability of the antioxidant is investigated and justified by the manufacturer; consequently, test for butylhydroxytoluene deleted.

*Identification*: chloroform replaced by methylene chloride and identification tests harmonised with that of *Wool fat (0134)*.

*Labelling*: section deleted (see general monograph *Substances for pharmaceutical use (2034)*).