COMMENTS CONCERNING SOME REVISED/ CORRECTED TEXTS PUBLISHED IN THE 6th EDITION

Here follows information concerning certain technical modifications to some revised/corrected texts adopted by the European Pharmacopoeia Commission at the November 2006 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

Quality systems: the statement formerly included under Production has been placed in a slightly modified form as a separate paragraph to give it more prominence.

General monographs: in response to many comments and queries, a paragraph indicating the complementary nature of general and individual monographs has been added.

Validation of pharmacopoeial methods: in response to many comments and queries, a statement has been added on validation of test methods; the methods are accepted by European regulatory authorities as validated so that a simple reference to the monograph is sufficient; there is no explicit statement for users, although it is implicit in regulatory documents; a clear statement has been added; validation by the analyst is not required, unless otherwise stated in the monograph (including any general method referred to).

References to regulatory documents: monographs and general chapters may contain references to regulatory documents (for example EMEA Notes for Guidance - see for example *5.14. Gene transfer medicinal products for human use*); inclusion of these references does not change the status of the documents referred to, nor their scope; an explicit statement to this effect has been added.

Chemical Abstracts Service (CAS) Registry Number: CAS numbers are included in monographs for information in the 6th Edition; the statement included in the General Notices is a condition of use of CAS numbers from the American Chemical Society.

Production: 'instructions' has been replaced by 'mandatory requirements', since this corresponds better to the contents of the Production sections in monographs and clarifies the status.

Powdered herbal drugs: a statement has been added to cover this new feature of monographs on herbal drugs.

Functionality-related characteristics of excipients: this paragraph has been revised in the light of developments in excipient monographs.

Reference standards: this section has been abbreviated and a reference to the new general chapter *5.12 Reference standards* added.

2.2.17. Drop point

The method is revised to include a description of the automated drop point method.

2.2.22. Atomic emission spectrometry

This general method has been revised to adapt it to current practice with more details of interferences and methodology.

2.2.23. Atomic absorption spectrometry

This general method has been revised to adapt it to the current technological developments in the field, with more details of graphite furnace atomic absorption, background correction and system suitability criteria such as linearity, recovery, repeatability and sensitivity.

2.6.9. Abnormal toxicity

Since difficulties have been reported in complying with the maximum weight limits for mice and guinea-pigs used, the maximum weight for mice has been increased to 24 g (range 17-24 g) and for guinea-pigs to 400 g (range 250-400 g).

5.1.4. Microbiological quality of pharmaceutical preparations

Part B (Harmonised method): in the special Ph. Eur. provision for herbal medicinal products consisting solely of one or more herbal drugs, a quantitative determination of *Escherichia coli* is required, but so far such quantification has not been described in detail. This text has been revised in order to include an appropriate method. The method can also be used in Part A (Method of the European Pharmacopoeia) under Category 4.

Interpretation of acceptance criteria for microbiological quality has been introduced for clarification as in the sign-off text (the interpretation is already given in chapter *2.6.12*).

DOSAGE FORMS

Eye preparations (1163)

Deliverable mass or volume: a systematic revision of the monographs prescribing this test is being carried out, in order to delete it; instead, a general requirement is added under Production.

Eye drops: the possibility to use multidose containers for eye drops that do not contain antimicrobial preservatives is now offered, provided these multidose containers are designed to avoid microbial contamination.

Semi-solid eye preparations: in the case of eye drops and eye lotions, a larger container than that prescribed in the monograph may be used, where justified and authorised; this possibility has been extended to semi-solid eye preparations.

Rectal preparations (1145)

Uniformity of dosage units: until this revision, the test for uniformity of dosage units applied only to solid single-dose preparations. However, certain preparations are presented as liquid or semi-solid preparations in single-dose containers, for which the total contents corresponds to a precise dose of the medicinal product (expressed as unit amount of active substance). The corresponding paragraph is modified to take these preparations into account.

Resistance to rupture: since chapter *2.9.24* has been deleted from the Ph. Eur., reference to this chapter is deleted from the section on suppositories.

Vaginal preparations (1164)

Uniformity of dosage units: until this revision, the test for uniformity of dosage units applied only to solid single-dose preparations. However, certain preparations are presented as liquid or semi-solid preparations in single-dose containers, for which the total contents corresponds to a precise dose of the medicinal product (expressed as unit amount of active substance). The corresponding paragraph is modified to take these preparations into account.

Resistance in rupture: since chapter *2.9.24* has been deleted from the Ph. Eur., reference to this chapter is deleted from the section on pessaries.

GENERAL MONOGRAPHS

Substances for pharmaceutical use (2034)

Related substances: the phrase "where justified and authorised" has been added for the application of the contents of table 2034.-1.

Microbiological quality: precisions have been added to clarify the application of Table 5.1.4.-2. – Acceptance criteria for microbiological quality of non-sterile substances for pharmaceutical use contained in the recently revised chapter *5.1.4. Microbiological quality of pharmaceutical preparations*.

Labelling: where appropriate, the label states the concentration of any added substance.

VACCINES FOR HUMAN USE

Influenza vaccine (surface antigen, inactivated, virosome) (2053)

Production: this monograph has been revised so that it covers 2 slightly different manufacturing processes.

Virosome size: this test has been revised in order to comply with the ISO guide 13321, and an upper limit on the polydispersity index has been included.

VACCINES FOR VETERINARY USE

Avian infectious bursal disease vaccine (inactivated) (0960)

Preparation of the vaccine: the monograph has been revised to delete vaccines grown in chickens from its scope, because no vaccine is produced in chickens anymore. Consequently, inactivation test C has also been deleted.

Serological potency test: as the serological threshold of 10 000 Ph. Eur. U./ml was too strict for current levels of protection, the potency and immunogenicity tests have been changed.

MONOGRAPHS

Adenosine (1486)

Related substances: an LC (Test B) has been introduced to cover impurities A, F, G and H in accordance with current policy as part of a special revision programme; the existing TLC (Test A) has been kept to cover impurities B, C, D and E.

Impurities: specified impurity G and other detectable impurities F and H have been added.

Allopurinol (0576)

Hydrazine: this substance can be used as starting material in the synthesis of allopurinol and a corresponding test (Impurity F) has been introduced to limit any residue which could be present.

Alteplase for injection (1170)

Identification and assay: since *alteplase CRS* is not available, the monograph has been revised in order to replace *alteplase CRS* by a suitable reference standard.

Amitriptyline hydrochloride (0464)

Identification by IR: replacement of the Ph. Eur. reference spectrum by a CRS in accordance with current policy.

Identification of the chlorides: replacement of reaction (b) by reaction (a) to avoid the use of potassium dichromate.

Second series identification: deleted to avoid the use of ether.

Related substances: replacement of the TLC by an LC.

Ascorbyl palmitate (0807)

Identification by IR: replacement of the Ph.Eur. reference spectrum by a CRS in accordance with current policy.

Benzbromarone (1393)

Identification by IR: the Ph.Eur. reference spectrum has been replaced by a CRS in accordance with current policy.

Boldo leaf (1396)

Identification B: an illustration of the powdered herbal drug has been added.

Calendula flower (1297)

Identification: an illustration of the powdered herbal drug has been added.

Castor oil, hydrogenated (1497)

Nickel: the method described in chapter *2.4.27. Heavy metals in herbal drugs and fatty oils* appears to be problematic when analysing fatty excipients, due to the use of sulphuric acid (excess of acid, very high pressure in the digestion vessel). A separate chapter has therefore been drafted (*2.4.31*), based on the original method which did not prescribe the use of sulphuric acid for the digestion.

Cefamandole nafate (1402)

Definition: the expression of content has been revised in order to reflect the fact that cefamandole is not to be considered as an impurity but as a participant to the activity of the substance.

Specific optical rotation: specifications have been updated based on the values found for substances used in approved medicinal products.

Cefepime dihydrochloride monohydrate (2126)

Impurity G: based on approved specifications and on stability data, the limit has been increased to 0.5 per cent.

Related substances: pH adjustment of the mobile phases is performed using 0.5 M KOH, as the pH before adjustment is below 5.0 according to the results of the collaborative trial for the establishment of the CRS.

Cetyl palmitate (1906)

Nickel: the method described in chapter *2.4.27. Heavy metals in herbal drugs and fatty oils* appears to be problematic when analysing fatty excipients, due to the use of sulphuric acid (excess of acid, very high pressure in the digestion vessel). A separate chapter has therefore been drafted (*2.4.31*), based on the original method which did not prescribe the use of sulphuric acid for the digestion.

Chlortalidone (0546)

Definition: the lower limit for content has been decreased as an LC assay is now prescribed. Characters: the substance shows polymorphism, so the corresponding statement has been added.

Identification: only the 1st identification has been kept as the substance is not used in pharmacies.

Appearance of solution: the test has been deleted because no formulations for injection exist on the market.

Optical rotation: the test has been deleted as no data on the optical rotation of the single enantiomer are available and the limit of detection of the test is therefore unknown.

Related substances. The TLC test has been replaced by an LC test that allows improved control of impurities.

Assay: the chromatographic method used for related substances has been introduced, as practical difficulties in the titration have been reported by users. More details on the development work are presented in Pharmeuropa Scientific Notes 2005-1.

Cholecalciferol (0072)

Definition: the upper limit for content has been tightened to 102.0 per cent as the assay is performed by LC.

Related substances: an LC test has been introduced in accordance with current policy.

Assay: LC conditions have been updated as the same method is used as for the related substances test.

Chondroitin sulphate sodium (2064)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Chymotrypsin (0476)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7 Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Clonidine hydrochloride (0477)

Related substances: TLC has been replaced by LC in accordance with current policy. Impurities: section introduced showing impurities controlled by LC.

Clozapine (1191)

Related substances: TLC has been replaced by LC in accordance with current policy as part of a special revision programme. Limits are based on current batch data.

Impurities: addition of specified impurity D.

Copper sulphate, anhydrous (0893)

Iron and Lead: the air-butane flame has been replaced by an air-acetylene flame. There is no commercial AAS-equipment available that allows the use of butane as fuel. Apparently butane was introduced to remove the risk of the formation of explosive copper acetylides. However, this risk may easily be overcome by cleaning the burner before any residues of copper acetylides become dry and dangerous. The use of acetylene with copper salts has been practised for many years without incident.

Copper sulphate pentahydrate (0894)

Iron and Lead: the air-butane flame has been replaced by an air-acetylene flame. There is no commercial AAS-equipment available that allows the use of butane as fuel. Apparently butane was introduced to remove the risk of the formation of explosive copper acetylides. However, this risk may easily be overcome by cleaning the burner before any residues of copper acetylides become dry and dangerous. The use of acetylene with copper salts has been practised for many years without incident.

Dalteparin sodium (1195)

Identification A: it is now clearly stated that *dalteparin sodium CRS* is the reference standard to be used.

Danaparoid sodium (2090)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Diclofenac potassium (1508)

Related substances: reference solution (b) has been modified, as impurity A is now produced by evaporation.

Diclofenac sodium (1002)

Related substances: reference solution (b) has been modified, as impurity A is now produced by evaporation.

Diethylcarbamazine citrate (0271)

Content: upper limit raised to 102.0 per cent.

Related substances and Assay: introduction of an LC method in accordance with current policy. The TLC for impurities A and B is maintained as these impurities are not UV absorbent. TLC silica gel plates are prescribed instead of TLC silica gel G plates which are less user-friendly.

Dipyridamole (1199)

Identification: deletion of the second series as the substance is probably not used in pharmacies. Related substances: replacement of the isocratic LC by a gradient LC that allows the control of additional impurities.

Dopamine hydrochloride (0664)

Definition: the limits of content have been tightened based on batch data.

Identification B: the prescription of a specific preparation for the IR was not necessary and has been deleted. Related substances: the current TLC has been replaced by an LC test in accordance with current policy as part of a special revision programme.

Storage: recommendations have been supplemented.

Enoxaparin sodium (1097)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, making it generally applicable. Identification A: it is now clearly stated that *enoxaparin sodium CRS* is the reference standard to be used.

Erythropoietin concentrated solution (1316)

Sialic acids: the range in the 2nd criterion for system suitability has been adjusted to correspond to the test limit.

Etodolac (1422)

Related substances: LC has been replaced by a more efficient method for a better reproducibility.

Eucalyptus leaf (1320)

Identification B: an illustration of the powdered herbal drug has been added.

Fenofibrate (1322)

Definition: limits of content have been enlarged as the assay is done by LC.

Fenoterol hydrobromide (0901)

Identification by IR: according to the general policy, the use of Ph. Eur. reference spectrum has been replaced by the use of a CRS.

Related substances: the control of impurities was performed using an LC test for impurity A (diastereoisomers) and a UV-photometric test for impurity B. In the framework of a special revision programme the existing LC test conditions have been slightly modified to cover impurity A and other related substances in one text. A new detection wavelength has been chosen.

Iron: according to the described protocol the limit has been corrected.

Impurities: specified impurity C has been added.

Fluorouracil (0611)

Identification: tests B and C have been deleted: the 2nd identification is not of practical relevance for this substance.

Related substances: TLC has been replaced by LC to cover impurities A, B, C, D and E. TLC has been kept for impurities F and G.

Impurities: this section has been introduced showing impurities controlled by LC and TLC tests.

Glucagon, human (1635)

The monograph has undergone a general revision to simplify the test procedures.

Related proteins: the composition of mobile phase A has been changed to improve the resolution between glucagon and carbamoylglucagon.

Glycerol dibehenate (1427)

Nickel: the method described in chapter *2.4.27. Heavy metals in herbal drugs and fatty oils* appears to be problematic when analysing fatty excipients, due to the use of sulphuric acid (excess of acid, very high pressure in the digestion vessel). A separate chapter has therefore been drafted (*2.4.31*), based on the original method which did not prescribe the use of sulphuric acid for the digestion.

Gonadotrophin, chorionic (0498)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Heparin calcium (0332)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Heparins, low-molecular-mass (0828)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the monograph *Substances for pharmaceutical use (2034)*, giving it general application. Identification A: for further clarity, 'CRS' has been replaced by 'reference standard' as it may either correspond to an EDQM CRS or to an in-house reference preparation, depending on whether a specific monograph and CRS exist or not.

Identification C: the criteria for compliance have been clarified, in particular with respect to the reference preparation to be used, whether the substance to be examined is covered by a specific monograph or not. Furthermore, the 25 per cent margin, which had originally been added because of the inherent difficulties in the determination of molecular mass distribution, has been deleted.

Heparin sodium (0333)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Human albumin solution (0255)

Protein composition: agarose gel has been added as an alternative to cellulose acetate. A collaborative study has shown that these methods, which are based on the same principles, give the same results. This collaborative study also demonstrated that the *albumin for electrophoresis BRP* batch 1 was still in agreement with its assigned value and was suitable to be used with both methods.

Human anti-D immunoglobulin (0557)

B19 virus DNA: in order to increase the level of quality with regard to B19 virus contamination, the test for B19 virus DNA must also be carried out on plasma pools from which albumin used as a stabiliser is derived.

Human anti-D immunoglobulin for intravenous administration (1527)

Definition: the test for anti-D antibodies prescribed in the monograph *Human normal immunoglobulin for intravenous administration (0918)* is not necessary in this particular anti-D product, since an assay of human anti-D immunoglobulin is carried out.

Production: in order to increase the level of quality with regard to B19 virus contamination, the test for B19 virus DNA must also be carried out on plasma pools from which albumin used as a stabiliser is derived.

Human plasma for fractionation (0853)

Production: in order to clarify the requirements for freezing plasma intended for the recovery of labile proteins, whether it is obtained by plasmapheresis or from whole blood, and in order to ensure homogeneous quality, the chamber temperature indication (- 30 °C or below) has been replaced by the following conditions: freezing conditions have to be validated to ensure that a temperature of - 25 °C or lower is attained at the core of each plasma unit within 12 h of placing in the freezing apparatus. These data are based on scientific studies on the freezing conditions for plasma. One of these studies is published in Pharmeuropa Scientific Notes 2006-1 (August 2006).

Human prothrombin complex (0554)

Assay: the main indication of the human prothrombin complex has changed. It is now more linked to the factor II (prothrombin) content than to the factor IX content. Furthermore, a factor II overload could lead to complications like thrombosis. For both reasons, this revision includes a ratio limit between factor II and factor IX of 0.70 to 1.65. This makes it possible to guarantee a better level of safety for the product.

Definition: in order to clarify the assay requirements, it is specifically stated that the range of 80 per cent to 125 per cent of the stated potency applies only when the coagulation factor content is stated by a single value. When the content is stated as a range, the estimated potency is not less than the lower limit and not greater than the upper limit of the stated range.

Labelling: since the statement regarding protein C and/or protein S is not necessary for use of the monograph, it has been deleted from the Labelling section; heparin and antithrombin amounts (where applicable) are both stated on the label for consistency with the Production section.

Hyaluronidase (0912)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Hydrochlorothiazide (0394)

Identification: IR spectra might show differences that disappear after recrystallisation: corresponding statement added.

Insulin, bovine (1637)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Insulin, porcine (1638)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Ketorolac trometamol (1755)

Related substances: henceforth, *ketorolac trometamol for peak identification CRS* contains impurity B and the *in situ* preparation of this impurity is unnecessary.

Lidocaine hydrochloride (0227)

Identification: the verification of the melting point in addition to the IR is unnecessary and has been deleted from the first series. The second series has been simplified to avoid the use of toxic reagents.

Related substances: the TLC for impurity A has been replaced by an LC, which allows the control of impurity A and other impurities.

Macrogol 15 hydroxystearate (2052)

Nickel: the method described in chapter *2.4.27. Heavy metals in herbal drugs and fatty oils* appears to be problematic when analysing fatty excipients, due to the use of sulphuric acid (excess of acid, very high pressure in the digestion vessel). A separate chapter has therefore been drafted (*2.4.31*), based on the original method which did not prescribe the use of sulphuric acid for the digestion.

Macrogol oleate (1618)

Acid value: limit raised to 2.0 per cent to take account of current production of macrogol oleate containing 5-6 moles of ethylene oxide per mole.

Matricaria flower (0404)

Total apigenin 7-glucoside: in this LC assay the washing and equilibration steps have been deleted from the gradient table, since they are considered to constitute standard laboratory practice.

Medroxyprogesterone acetate (0673)

Related substances: based on information concerning approved products, a correction factor of 1.5 for impurity A has been added and the corresponding limit has been increased accordingly; the limits for impurity D and for the total have been increased in light of current batch data; impurities A and I have been introduced into the system suitability CRS to allow identification of the corresponding peaks, and their relative retentions have been slightly modified based on experimental data. Impurities: the structure of impurity I has been corrected because the wrong epimer (epimer 2) had been introduced in the previous version.

Metamizole sodium (1346)

Definition: the usual higher limit of content for titration is now prescribed.

Methenamine (1545)

Identification by IR: replacement of the Ph.Eur. reference spectrum by a CRS in accordance with current policy.

Monoclonal antibodies for human use (2031)

Production: requirements with regard to the acceptability of cell lines have been aligned with that of the ICH Q5A guideline.

Nadroparin calcium (1134)

Identification A: it is now clearly stated that *nadroparin sodium CRS* is the reference standard to be used.

Nonoxinol 9 (1454)

Identification by IR: replacement of the Ph.Eur. reference spectrum by a CRS in accordance with current policy.

Noradrenaline hydrochloride (0732)

Related substances: the concentration of *noradrenaline impurity F CRS* has been increased in the reference solution to facilitate its peak identification in the chromatogram.

Noradrenaline tartrate (0285)

Related substances: the concentraton of *noradrenaline impurity F CRS* has been increased in the reference solution to facilitate its peak identification in the chromatogram.

Oregano (1880)

Definition: it has been revised in order to express the limit for thymol and carvacrol in the more usual way, with reference to the essential oil.

Palmitic acid (1904)

Nickel: the method described in chapter *2.4.27. Heavy metals in herbal drugs and fatty oils* appears to be problematic when analysing fatty excipients, due to the use of sulphuric acid (excess of acid, very high pressure in the digestion vessel). A separate chapter has therefore been drafted (*2.4.31*), based on the original method which did not prescribe the use of sulphuric acid for the digestion.

Pancreas powder (0350)

Definition: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Paraffin, hard (1034)

Identification by IR: replacement of the Ph.Eur. reference spectrum by a CRS in accordance with current policy.

Parnaparin sodium (1252)

Identification A: it is now clearly stated that *parnaparin sodium CRS* is the reference standard to be used.

Paroxetine hydrochloride, anhydrous (2283)

Production: impurity G can be controlled by LC with UV detection and reference to LC/MS has been deleted.

Residual solvents: a limit higher than 0.5 per cent has been authorised for 2-propanol and a specific limit has been included in the monograph for this solvent.

Paroxetine hydrochloride hemihydrate (2018)

Production: impurity G can be controlled by LC with UV detection and reference to LC/MS has been deleted.

Pentaerythrityl tetranitrate, diluted (1355)

Identification: the previous test A was not appropriate for this substance and has been deleted. Related substances: the previous method did not adequately control impurity C and has been replaced.

Assay: the LC from the test for related substances is used.

Pepsin powder (0682)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Perindopril *tert*-butylamine (2019)

Characters: the solubility in methylene chloride has been adjusted according to the observations made during routine quality control.

Identification B: the description of the preparation has been deleted in accordance with current policy.

Stereochemical purity: the description of the test has been modernised and additional diastereoisomers have been included in the list as other detectable impurities.

Related substances: the LC method has been replaced by a more robust and easy-to-use LC method, which also allows the separation and detection of new degradation impurities; a peak-to-valley ratio criterion for impurities B and K has been introduced; degradation impurities J and K, and potential synthesis impurities L, M, N and O not normally found in the batches, are added as other detectable impurities.

Pholcodine (0522)

Definition: content upper limit increased.

Identification: tests B and C deleted as they are not of practical relevance for this substance; replacement of the IR spectrum by a CRS in accordance with current policy.

Related substances: TLC replaced by LC in accordance with current policy.

Morphine: deleted, replaced by the LC.

Impurities: section introduced showing impurities controlled by LC.

Promethazine hydrochloride (0524)

Related substances: TLC has been replaced by LC in accordance with current policy as part of a special revision programme. Limits are based on current batch data.

Riboflavin (0292)

Definition: a statement has been added indicating that the monograph applies to riboflavin produced by fermentation. This implies that the thresholds given under Related substances in the general monograph *Substances for pharmaceutical use (2034)* do not apply to this individual monograph.

Related substances: within the framework of a special revision programme, the TLC test for lumiflavine has been replaced by an LC test for Related substances. The limits proposed are based on batch data from commercial substances. So far, no data have been obtained from manufacturers producing riboflavin by chemical synthesis. In the absence of such information, the existing monograph will be restricted to riboflavin produced by fermentation. Impurities: specified impurities B, C and D have been added.

Ribwort plantain (1884)

Identification B: an illustration of the powdered herbal drug has been added.

Rice starch (0349)

Characters, Identification, pH, Iron, Foreign matter, Loss on drying, Sulphated ash, Oxidising substances, Sulphur dioxide: general revision within the framework of the harmonisaton with JP and USP.

Sodium acetate trihydrate (0411)

Reducing substances: the test has been revised as it did not give satisfactory results.

Sodium calcium edetate (0231)

Identification C: only reaction (b) of calcium is suitable.

Identification D: the method is replaced by the one approved in the framework of international harmonisation.

Sodium fluoride (0514)

Assay: the current method often causes problems due to the unsatisfactory solubility of the substance in the titration medium. Titration with lanthanum nitrate in aqueous medium is now used.

Sodium hyaluronate (1472)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Squalane (1630)

Nickel: the method described in chapter *2.4.27. Heavy metals in herbal drugs and fatty oils* appears to be problematic when analysing fatty excipients, due to the use of sulphuric acid (excess of acid, very high pressure in the digestion vessel). A separate chapter has therefore been drafted (*2.4.31*), based on the original method which did not prescribe the use of sulphuric acid for the digestion.

Tinzaparin sodium (1271)

Identification A: it is now clearly stated that *tinzaparin sodium CRS* is the reference standard to be used.

Trimipramine maleate (0534)

Appearance of solution: trimipramine maleate is not used in parenteral dosage forms; the test has therefore been deleted. Related substances: TLC has been replaced by an LC in accordance with current policy as part of a special revision programme. Limits are based on current batch data.

Impurities: a section describing the impurities controlled by LC has been added.

Trypsin (0694)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Urofollitropin (0958)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Urokinase (0695)

Production: all general statements related to contamination by infectious agents have been deleted. The approach to viral contamination is now addressed in general chapter *5.1.7. Viral safety*, which applies wherever a substance of human or animal origin is used in the preparation of a medicinal product. A reference to chapter *5.1.7* has been included in the general monograph *Substances for pharmaceutical use (2034)*, giving it general application.

Warfarin sodium (0698)

Identification: the second series has been deleted since it has no practical application for this substance.

Related substances: the TLC test has been replaced by LC in accordance with current policy.

Warfarin sodium clathrate (0699)

Identification: the second series has been deleted since it has no practical application for this substance.

Related substances: the TLC test has been replaced by LC in accordance with current policy. Water: the limit has been raised to 0.3 per cent. Batch data indicate that the limit of 0.1 per cent is too strict and stability data indicate that a limit of 0.3 per cent is acceptable.

Yohimbine hydrochloride (2172)

Related substances: a new impurity has been found during establishment of the CRS: impurity G. This impurity has been added as a specified impurity of unknown structure, and quantified in the sum of A and G. Moreover, a temperature of 40 °C is indicated for the column.