

DRAFT AMENDMENTS FOR ADDENDUM 2011 OF IP 2010

UPDATED ON: 28.02.2011

The IPC has received inputs from its stakeholders on IP 2010 which require upgradation/change. The draft amendments (PROPOSED) are put on the website (www.ipc.gov.in) for comments of the users. It is expected to have your comments within 21 days.

2.2.9 Microbiological Contamination in Nonsterile Products

Table 1. Page 39

Delete "Remarks column"

Medium 8. Rappaport Vassiliadis Salmonella Enrichment broth`

Last sentence

Change **from:** pH 5.2± 2 **to:** pH 5.2± 0.2

Medium 9. Wilson and Blair's BBS Agar

Add the following before 'Complete Medium'

Solution (iii) Nutrient Agar solution

Peptone 1.0g

Beef Extract 1.0g

Sodium Chloride 0.5g

Agar 2.0g

Purified water 100ml

Mix thoroughly, sterilise and cool to 45° to 50°

Medium 10. GN Broth

Last sentence

Delete: 'Cool to 50°, mix, pour into Petri dishes.'

2.4.14 Liquid Chromatography

General. *Secondary peaks*

Insert the following at the end

"peaks identified as due to the counter-ion and / or other excipients including preservatives in the substance under examination may also be excluded"

2.4.26 Solubility

Allantoin. Page 148

Change **to:** Slightly soluble in *water*; very slightly soluble in *ethanol*.

Lansoprazole. Page 159

Change **to:** Freely soluble in *dimethylformamide*; practically insoluble in *water*.

Tolterodine Tartrate. Page 170

Change **from:** Soluble in *water*. **to:** Slightly soluble in *ethanol* (95 per cent) and sparingly soluble in *methanol*.

Zoledronic Acid. Page 171

Change **from:** Sparingly soluble in *water*. **to:** Slightly soluble in *water*.

2.5.6 Contents of Packaged Dosage Forms. Page 194

Ointments, Creams, Pastes, Granules and Powder for Oral Liquids. Para 2, last line

Change **from:** labelled **to:** labelled amount

Para 3, line 7

Change **from:** 95 per cent **to:** 95.5 per cent

Liquids and suspensions. Para 4, line 9

Change **from:** milord **to:** ml or

4.2. GENERAL REAGENTS

Page. 569

Insert the following before **Barbaloin**

Azomethine H Solution. Dissolve 0.45 g of *azomethine H* and 1 g of *ascorbic acid* in *water* with the aid of gentle heat and add sufficient *water* to produce 100 ml.

Page. 613

Insert the following before **Sodium phosphate, Tribasic**

Sodium phosphate, Monobasic; Sodium Biphosphate; Sodium Dihydrogen Phosphate; Acid Sodium Phosphate; Monosodium Orthophosphate: $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O} = 138.0$
General reagent grade of commerce.

Tetrabutylammonium Hydroxide. Page 616

Change to: **Tetrabutylammonium Hydroxide:** $\text{C}_{16}\text{H}_{37}\text{NO}, 30\text{H}_2\text{O} = 800$

General laboratory reagent grade of commerce.

Contains not less than 98.0 per cent w/v of $\text{C}_{16}\text{H}_{37}\text{NO}, 30\text{H}_2\text{O}$.

Assay- Dissolve 1 g in 100 ml of *water* and titrate immediately with 0.1M *hydrochloric acid VS* determining the end point potentiometrically.

1 ml of 0.1M *hydrochloric acid VS* is equivalent to 0.08 g of $\text{C}_{16}\text{H}_{37}\text{NO}, 30\text{H}_2\text{O}$.

Page. 621

Insert the following before **Zinc, Activated**

Zinc Acetate: $(\text{C}_2\text{H}_3\text{O}_2)_2\text{Zn}, 2\text{H}_2\text{O} = 219.5$

General reagent grade of commerce.

mp, about 237°.

Zinc Acetate Solution: Mix 600 ml of *water* with 150 ml of *glacial acetic acid*, add 54.9 g of *zinc acetate* and stir to dissolve. Continue stirring while adding 150 ml of 13.5M *ammonia*, cool to room temperature, adjust to pH 6.4 with 6M *ammonia* and add sufficient *water* to produce 1000 ml.

0.25 M zinc acetate: Mix 600 ml of *water* with 150 ml of *glacial acetic acid* and 54.9 g of *zinc acetate*, stir to dissolve. While stirring, add 150 ml of *ammonium hydroxide*, cool to room temperature, and adjust to pH of 6.4 with *ammonium hydroxide* and dilute to 1000 ml with *water*.

MONOGRAPHS

Inhalation Preparations. Page 726

Powders for Inhalation. page 740

Delete the requirement “**Uniformity of content**”

Aciclovir. Page 775

Related substances. *Reference solution*

Change to: *Reference solution.* A 0.005 per cent w/v solution of 2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl acetate RS (*aciclovir impurity A RS*) in *dimethyl sulphoxide*.

Adrenaline Tartrate. Page 778

Specific optical rotation. Line 2

Change from: 4.0 per cent w/v solution to: 4.0 per cent w/v solution of residue obtained in identification test

Amoxicillin and Potassium Clavulanate Tablets. Page.819

Assay. Chromatographic system, line 4

Change from: *sodium phosphate* to: *sodium phosphate, monobasic*

Atorvastatin Tablets. Page 851

Related substances.

Solvent mixture. Change **from:** A mixture of 40 volumes of *acetonitrile* and 60 volumes of buffer **to:** A mixture of 40 volumes of *acetonitrile* and 60 volumes of *water*

Azithromycin Oral Suspension. Page 860

Related substances. *Test solution*, line 3

Change **from:** 25 ml **to:** 50 ml

Chromatographic system, line 16

Change **from:** 50 µl **to:** 100 µl

Betamethasone Lotion. Page 904

Usual strength

Change **from:** 0.05 per cent w/w **to:** 0.5 per cent w/v

Delete the requirement “**Other tests.**”

Bromhexine Hydrochloride. Page 922

Identification. B

Change **from:** In the test for Related Substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution (c). **to:** In the test for Related Substances, the principal peak in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with reference solution (b).

Related substances. *Reference solution (b).*

Change **from:** Dilute 1.0 ml of the test solution to 100.0 ml with *methanol*. Dilute 1.0 ml of this solution to 10.0 ml with the same solvent. **to:** A 0.0005 per cent w/v solution of *bromhexine hydrochloride RS* in *methanol*.

Last para, line 5

Change **from:** the area of one such peak is not more than **to:** the area of not more than one such peak is more than

Bromocriptine Mesylate. Page 923

Identification.

Change to: *Test A may be omitted if tests B, C and D are carried out. Tests B, C and D may be omitted if test A is carried out.*

A. Determine by infrared absorption spectrophotometry in a mineral oil dispersion (2.4.6). Compare the spectrum with that obtained with *bromocriptine mesylate RS* or with the reference spectrum of bromocriptine mesylate.

B. Dissolve 5 mg in 5 ml of *methanol* and dilute to 100 ml with 0.01 M *hydrochloric acid*. The resulting solution, when examined in the range 230 nm to 360 nm (2.4.7) shows an absorption maximum at about 305 nm and a minimum at about 270 nm; absorbance at about 305 nm, 0.60 to 0.68.

C. To about 0.1 g add 5 ml of 2 M *hydrochloric acid*, shake for 5 minutes, filter and add 1 ml of a 6 per cent w/v solution of *barium chloride* to the filtrate; it remains clear. Mix another 0.1 g with 0.5 g of *anhydrous sodium carbonate* and ignite until a white residue is obtained. After cooling, dissolve the residue in 5 ml of water (solution A); solution A gives the reactions of sulphates (2.3.1).

D. Solution A gives reaction A of bromides (2.3.1).

Change **Related substances to:**

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. A mixture of 50 volumes of *chloride buffer pH 2.0* and 50 volumes of *methanol*.

Test solution. Dissolve 0.5 g of the substance under examination in 5.0 ml of *methanol* and dilute to 10.0 ml with *chloride buffer pH 2.0*.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dilute 1.0 ml of the reference solution (a) to 10.0 ml with the solvent mixture.

Reference solution (c). Dissolve the contents of a vial of *bromocriptine mesylate for system suitability RS* (containing bromocriptine impurities A and B) in 1.0 ml of the solvent mixture.

Chromatographic system

- a stainless steel column 12 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (5µm),
- mobile phase: A. a 0.079 per cent w/v solution of *ammonium carbonate*,
B. *acetonitrile*,
- a linear gradient programme using the conditions given below,
- flow rate. 2 ml per minute,
- spectrophotometer set at 300 nm,
- injection volume. 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0-30	90- 40	10-60
30-45	40	60

Use the chromatogram supplied with *bromocriptine mesylate for system suitability RS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B. The relative retention time with reference to bromocriptine for bromocriptine impurity c is about 1.2.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to 2-bromodehydro- α -ergocriptine (bromocriptine impurity A) and α -ergocriptine (bromocriptine impurity B) is not less than 1.1.

Inject the test solution and reference solutions (a) and (b). In the chromatogram obtained with the test solution, the area of any secondary peak corresponding to bromocriptine impurity A is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent), the area of secondary peak corresponding to bromocriptine impurity C is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent). The sum of the areas of all the secondary peaks is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent) (except the peak due to bromocriptine impurity A).

Bromocriptine Capsules. Page 924

Related substances Change to:

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Note- Prepare the solutions in subdued light and immediately before use. Apply the test solution as the last solution and develop the chromatograms immediately in an unsaturated tank.

Mobile phase. A mixture of 0.1 volumes of 13.5M *ammonia*, 1.5 volumes of *water*, 3 volumes of *propan-2-ol*, 88 volumes of *dichloromethane* and 100 volumes of *ether*.

Test solution. Shake a quantity of the contents of the capsules containing about 20 mg of bromocriptine with 10 ml of *methanol* for 20 minutes and centrifuge.

Reference solution (a). Dilute 1 ml of the test solution to 10 ml with *methanol*.

Reference solution (b). Dilute 3 ml of the test solution to 100 ml with *methanol*.

Reference solution (c). Dilute 1 ml of the test solution to 100 ml with *methanol*

Reference solution (d). Dilute 1 ml of the test solution to 200 ml with *methanol*.

Reference solution (e). A 0.023 per cent w/v solution of *bromocriptine mesilate RS* in *methanol*.

Apply to the plate 50 µl of each solution. Allow the mobile phase to rise 15 cm. Dry the plate in a current of cold air, spray with *ammonium molybdate solution* and heat at 100° until bands appear (about 10 minutes). Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (b) (3.0 per cent), not more than one such secondary spot is more intense than the chromatogram obtained with reference solution (c) (1.0 per cent) and not more than two such secondary spots are

more intense than the chromatogram obtained with reference solution (d) (0.5 per cent). Ignore the spot within 20 mm of the line of application.

Bromocriptine Tablets. Page 925

Related substances Change to:

Related substances. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel G*.

Solvent mixture. Equal volumes of *chloroform* and *methanol*.

Mobile phase. A mixture of 0.1 volumes of *13.5M ammonia*, 1.5 volumes of *water*, 3 volumes of *propan-2-ol*, 88 volumes of *dichloromethane* and 100 volumes of *ether*.

Test solution. Shake a quantity of the powdered tablets containing about 10 mg of bromocriptine with 25 ml of the solvent mixture for 30 minutes, filter and wash the residue with two 5 ml quantities of the solvent mixture. Evaporate the filtrate and washings to dryness at 25° at a pressure of 2 kPa, dissolve the residue in 2 ml of the solvent mixture and centrifuge.

Reference solution (a). Dilute 1 ml of the test solution to 10 ml with the solvent mixture.

Reference solution (b). Dilute 3 ml of reference solution (a) to 10 ml with the solvent mixture

Reference solution (c). Dilute 1 ml of reference solution (a) to 10 ml with the solvent mixture.

Reference solution (d). Dilute 1 ml of reference solution (a) to 20 ml with the solvent mixture.

Reference solution (e). A 0.055 per cent w/v solution of *bromocriptine mesilate RS* in the solvent mixture.

Apply to the plate 20 µl of each solution. Allow the mobile phase to rise 15 cm. Dry the plate in air, spray with *ammonium molybdate solution* and heat at 100° until spots appear (about 10 minutes). Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (b) (3.0 per cent), not more than one such secondary spot is more intense than the spot in the chromatogram obtained with reference solution (c) (1.0 per cent) and not more than two secondary spots are more intense than the spot in the chromatogram obtained with reference solution (d) (0.5 per cent). Ignore the spot within 20 mm of the line of application.

Calcitriol. Page 960

Dose.

Change **from:** 0.5µg **to:** 100 IU to 1000 IU

Assay. Chromatographic system, line 1

Change **from:** packed with **to:** packed with octadecylsilane bonded to porous silica

Calcium Carbonate. Page 961

Category.

Change **to:** Antacid; Pharmaceutical aid (excipient)

Calcium Stearate. Page 971

Para 2

Change **to:** Calcium Stearate contains the equivalent of not less than 9.0 per cent and not more than 10.5 per cent of calcium oxide (CaO). Stearic acid in the fatty acid fraction is not less than 40.0 per cent and sum of stearic acid and palmitic acid in the fatty acid fraction is not less than 90.0 per cent.

Insert the following before **Identification**

Description. A white or almost white crystalline powder.

Cefadroxil. Page 998

Related substances. After chromatographic system, para 1

Change from: Inject reference solution (c). The relative retention time with reference to cefadroxil for dimethylformamide is about 0.4 and for dimethylacetamide is about 0.75. The test is not valid unless the resolution between the peaks due to cefadroxil impurity A and C is not less than 5.0. In the chromatogram obtained with reference solution (e) signal- to- noise ratio for the second peak is not less than 10. **to:** Inject reference solution (d). The relative retention time with reference to cefadroxil for dimethylformamide is about 0.4 and for dimethylacetamide is about 0.75. The test is not valid unless the resolution between the peaks due to cefadroxil impurity A and B is not less than 5.0. In the chromatogram obtained with reference solution (e) signal- to- noise ratio for the second peak is not less than 10

Ceftazidime. Page 1021

Change the test of Pyridine **to**.

Pyridine. Not more than 500 ppm.

Determine by liquid chromatography (2.4.14).

NOTE—Prepare the solutions immediately before use.

Test solution. Dissolve 0.5 g of the substance under examination in 100 ml of 10 per cent v/v solution of *phosphate buffer pH 7.0*.

Reference solution (a). Dissolve 1 g of *pyridine* in 100.0 ml of *water*. Dilute 5.0 ml of this solution to 200.0 ml with *water*. To 1.0 ml of the solution, add 10 ml of *phosphate buffer pH 7.0* and further dilute to 100 ml with *water*.

Reference solution (b). Dilute 1.0 ml of the test solution to 200.0 ml of 10 per cent v/v solution of *phosphate buffer pH 7.0*. To 1.0 ml of the solution, add 20 ml of reference solution (a) and further dilute to 200 ml with a 10 per cent v/v solution of *phosphate buffer pH 7.0*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 8 volumes of 2.88 per cent w/v solution of *ammonium dihydrogen orthophosphate* in *water*, previously adjusted to pH 7.0 with *ammonia*, 24 volumes of *acetonitrile* and 68 volumes of *water*,
- flow rate. 1 ml per minute,
- spectrophotometer set at 255 nm,
- injection volume. 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to ceftazidime and ceftazidime impurity F is not less than 7.0.

Inject reference solution (a). The test is not valid unless the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the test solution and reference solution (a).

Cefuroxime Sodium. Page 1028

Para 2, line 2

Change **from:** 90.0 per cent **to:** 96.0 per cent

Line 3

Change **from:** 105.0 per cent **to:** 102.0 per cent

Chlordiazepoxide. Page 1054

Related substances. After chromatographic system, Para 1 and 2

Change **to:** Inject reference solution (b). The test is not valid unless the resolution between the peaks due to chlordiazepoxide impurity A and chlordiazepoxide is not less than 5.0. The relative retention time with reference to chlordiazepoxide for 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one 4-oxide (chlordiazepoxide impurity A) is about 0.7; for 6-chloro-2-(chloromethyl)-4-phenylquinazoline 3-oxide (chlordiazepoxide impurity B) is about 2.3; for aminochlorobenzophenone (chlordiazepoxide impurity C) is about 3.9.

Inject the test solution, reference solution (a) and (c). Run the chromatogram 6 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of the peak due to chlordiazepoxide impurity A, B, for each impurity, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of the peak due to chlordiazepoxide impurity C is not more than the

area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent). The area of any other secondary peak, for each impurity, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and sum of areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Chlorhexidine Gluconate Solution. Page 1057

Weight per ml. Line 1,
Change **from:** 20° **to:** 25°

Chloroquine Sulphate Tablets. Page 1066

Assay. Line 9
Change **from:** 0.0436 g **to:** 0.0209 g

Cinnarizine Tablets. Page 1090

Insert the test before **Related substances.**

Dissolution (2.5.2).

Apparatus No. 1,

Medium. 900 ml of gastric fluid simulated (without pepsin) TS prepared by dissolving 2.0 g of *sodium chloride* in 80 ml of 1M *hydrochloric acid* and sufficient *water* to make 1000 ml,

Speed and time. 100 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, suitably diluted if necessary, at the maximum at about 253 nm (2.4.7). Calculate the content of C₂₆H₂₈N₂ in the medium from the absorbance obtained from a solution of known concentration of *cinnarizine RS*.

D. Not less than 70 per cent of the stated amount of C₂₆H₂₈N₂.

Clozapine. Page 1126

Related substances. Change to:

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. A mixture of 20 volumes of *water* and 80 volumes of *methanol*.

Test solution. Dissolve 75 mg of the substance under examination in 80 ml of *methanol* and dilute to 100.0 ml with *water*.

Reference solution. Dilute 1.0 ml of the test solution to 10.0 ml with the solvent mixture. Further dilute 1.0 ml of this solution to 100.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 12.5 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: A. a mixture of 10 volumes of *acetonitrile*, 10 volumes of *methanol* and 80 volumes of buffer solution prepared by dissolving 2.04 g of *potassium dihydrogen phosphate* in 1000 ml of *water* adjusted to pH 2.4 with *orthophosphoric acid*,
B. a mixture of 40 volumes of *acetonitrile*, 40 volumes of *methanol* and 20 volumes of buffer solution prepared by dissolving 2.04 g of *potassium dihydrogen phosphate* in 1000 ml of *water* adjusted to pH 2.4 with *orthophosphoric acid*,
- flow rate. 1.2 ml per minute,
- a linear gradient programme using the conditions given below,
- spectrophotometer set at 257 nm,
- injection volume. 20 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0 – 4	100	0
4 – 24	100 → 0	0 → 100
24 – 29	0	100

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 10.0 per cent. The relative retention time with reference to clozapine for 8-chloro-11-(piperazin-1-yl)-5H-dibenzo[*b,e*][1,4]diazepine (clozapine impurity C) is about 0.9, for 1-[2-[(2-amino-4-chlorophenyl)amino]benzoyl]-4-methylpiperazine (clozapine impurity D) is about 1.1, for 8-chloro-5,10-dihydro-11H-dibenzo[*b,e*][1,4]diazepin-11-one (clozapine impurity A) is about 1.6, for 11,11'-(piperazine-1,4-diyl)bis(8-chloro-5H-dibenzo[*b,e*][1,4]diazepine) (clozapine impurity B) is about 1.7.

Inject the test solution and the reference solution. In the chromatogram obtained with the test solution, the area of the peak due to clozapine impurity A is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent). The area of the peak due to clozapine impurity B and D, for each impurity, is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent), the area of the peak due to clozapine impurity C is not more than three times the area of the principal peak in the chromatogram obtained with the reference solution (0.3 per cent). The area of other secondary peaks for each impurity is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent). The sum of all the secondary peaks is not more than 6 times the area of the principal peak in the chromatogram obtained with the reference solution (0.6 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Danazol Capsules. Page 1161

Dissolution. Line 1

Change **from:** Apparatus No. 2 **to:** Apparatus No. 1

Desferrioxamine Mesylate. Page 1167

Identification

Change **to:**

Test A may be omitted if tests B and C are carried out. Tests B and C may be omitted if test A is carried out.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *desferrioxamine mesylate RS* or with the reference spectrum of desferrioxamine mesylate.

B. Dissolve 5 mg in 5 ml of *water*, add 2 ml of a 0.5 per cent w/v solution of *tribasic sodium phosphate*, mix and then add 0.5 ml of a 2.5 per cent w/v solution of *sodium 1,2-naphthoquinone-4-sulphonate*; a blackish brown colour is produced.

C. Dissolve 0.1 g in 5 ml of 2 M *hydrochloric acid* and add 1 ml of *barium chloride solution*; the solution remains clear. In a porcelain crucible mix 0.1 g with 1 g of *anhydrous sodium carbonate*, heat and ignite over a Bunsen flame. Allow to cool, dissolve the residue in 10 ml of *water* by heating if necessary and filter; the filtrate gives reaction A of sulphates (2.3.1).

Desferrioxamine Injection. Page 1169

Identification

Change **to:**

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *desferrioxamine mesylate RS* or with the reference spectrum of desferrioxamine mesylate.

Dextromethorphan Hydrobromide. Page 1186

Identification. C

Change **from:** In the test for Related substances, the principal spot in the chromatogram obtained with test solution (b) corresponds to that in the chromatogram obtained with reference solution (c). **to:** In the test for Related substances, the principal peak in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

Related substances. *Reference solution.* Lines 1 and 2

Change **to:** A 0.0005 per cent w/v solution of *dextromethorphan hydrobromide RS* in the mobile phase.

Last para

Change **to**: Inject the test solution and the reference solution. Run the chromatogram twice the retention time of the principal peak. In the chromatogram obtained with the test solution the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent) and the area of not more than one such peak is more than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.25 per cent). The sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Diclofenac Sodium. Page.1199

Heavy metals. Line 1

Change **from**: 1.0 g **to**: 2.0 g

Diclofenac Injection. Page 1200

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a suitable volume of the injection containing 50 mg of Diclofenac Sodium to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (a). A 0.005 per cent w/v solution of *diclofenac sodium RS* in the mobile phase.

Reference solution (b). A solution containing 0.0005 per cent w/v of *diclofenac sodium RS* and 0.0005 per cent w/v of *1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one RS (diclofenac impurity A RS)* in the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 34 volumes of a mixture of equal volumes of a 0.1 per cent w/v solution of *orthophosphoric acid* and a 0.16 per cent w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 66 volumes of *methanol*,
- flow rate. 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume. 10 µl.

Inject reference solution (b). The test is not valid unless the resolution between diclofenac and diclofenac impurity A is not less than 6.5.

Inject the test solution and reference solution (a).

Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ in the injection.

Diclofenac Tablets. Page 1200

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Shake 10 tablets with 700 ml of *methanol (50 per cent)* for 30 minutes with the aid of ultrasound, add sufficient mobile phase to produce 1000 ml, mix and filter. Dilute the filtrate with the mobile phase to produce a solution containing 0.005 per cent w/v of Diclofenac Sodium.

Reference solution (a). A 0.005 per cent w/v solution of *diclofenac sodium RS* in the mobile phase.

Reference solution (b). A solution containing 0.0005 per cent w/v of *diclofenac sodium RS* and 0.0005 per cent w/v of *1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one RS (diclofenac impurity A RS)* in the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 34 volumes of a mixture of equal volumes of a 0.1 per cent w/v solution of *orthophosphoric acid* and a 0.16 per cent w/v solution of *sodium dihydrogen orthophosphate*, adjusted to pH 2.5, and 66 volumes of *methanol*,
- flow rate. 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume. 10 µl.

Inject reference solution (b). The test is not valid unless the resolution between diclofenac and diclofenac impurity A is not less than 6.5.

Inject the test solution and reference solution (a).

Calculate the content of $C_{14}H_{10}Cl_2NNaO_2$ in the tablet.

Activated Dimethicone. Page.1230

Acidity. Line 3

Change **from:** 0.15 ml **to:** 3.0 ml

Disodium Edetate. Page 1234

Impurity A. Chromatographic system, line 2

Add the following at the end

“with a specific surface area of 120 m²/g and a pore size of 25 nm”

Iron.

Change **from:** **Iron** (2.3.14). 20 ml of a 2.5 per cent w/v solution complies with the limit test for iron (80 ppm). Add 0.25 g of *calcium chloride* to each solution before adding mercaptoacetic acid. **to:** **Iron** (2.3.14). 10 ml of a 1.25 per cent w/v solution complies with the limit test for iron (80 ppm). Add 0.25 g of *calcium chloride* to each solution before adding *thioglycollic acid*.

Docetaxel Injection. Page 1243

Para 1

Change **from:** The injection is constituted by dissolving the contents of the sealed container in the requisite amount of sterile Water for Injections in accordance with the manufacturer’s instructions, immediately before use. **to:** The injection is constituted by dissolving the contents of the sealed container in accordance with the manufacturer’s instructions, immediately before use.

pH.

Change **from:** **pH** (2.4.24). 2.5 to 3.5, determined in a solution constituted as directed in the label, in 15.3 per cent v/v solution of *absolute ethanol*. **to:** **pH** (2.4.24). 2.5 to 4.5, determined in a solution constituted by mixing 1 vial of the concentrate with 15.3 per cent v/v *absolute ethanol*, as directed on the label.

Related substances. Test solution

Change **from:** Reconstitute 1 vial of sample with 1 vial of solvent. Weigh accurately 1.25 g of the reconstituted solution and dilute to 25.0 ml with the solvent mixture. **to:** Reconstitute 1 vial of sample with 1 vial of solvent. Dilute the reconstituted solution to obtain a solution containing about 0.5 mg per ml of docetaxel.

Chromatographic system, line 1

Change **from:** 50 cm **to:** 25 cm

Assay. Test solution

Change **from:** Reconstitute 1 vial of sample with 1 vial of solvent. Weigh accurately 1.25 g of the reconstituted solution and dilute to 50.0 ml with the mobile phase. **to:** Reconstitute 1 vial of sample with 1 vial of solvent. Dilute the reconstituted solution to obtain a solution containing about 0.25 mg per ml of docetaxel.

Chromatographic system, line 1

Change **from:** 50 cm **to:** 25 cm

Donepezil Hydrochloride. Page.1248

After structure

Change **from:** Mol. Wt. 415.5 **to:** Mol. Wt. 416

Related substances. Reference solution (a), line 1

Change **from:** 0.1 per cent **to:** 0.01 per cent

After chromatographic system

Line 3

Change **from**: 0.5 times **to**: 5 times

Line 6

Change **from**: twice **to**: 20 times

Assay. Line 6

Change **from**: 0.04155 **to**: 0.0416 per cent

Enoxaparin Sodium. Page 1276

Sodium.

Change **to**: **Sodium.** 11.3 per cent to 13.5 per cent.

Determine by atomic absorption spectrometry (2.4.2, Method A).

Test solution. Dissolve 50 mg in 0.1 M hydrochloric acid containing 0.127 per cent w/v solution of caesium chloride and dilute to 100.0 ml with the same solvent.

Reference solutions. Prepare reference solutions (25 ppm, 50 ppm and 75 ppm) using sodium standard solution (200 ppm Na) diluted with 0.1 M hydrochloric acid containing 0.127 per cent w/v solution of caesium chloride.

Source Sodium hollow-cathode lamp.

Wavelength 330.3 nm.

Atomisation device Flame of suitable composition (for example, 11 litres of air and 2 litres of acetylene per minute).

Nitrogen. Line 1

Change **from**: 1.8 to 2.5 per cent, **to**: 1.8 to 2.5 per cent, Method E,

Benzyl alcohol. *Internal standard solution.* Line 1

Change **from**: 10.0 per cent **to**: 0.1 per cent

Enoxaparin Injection. Page.1279

Free sulphate. Line 2

Change **from**: liquid chromatography (2.4.14) **to**: ion chromatography (2.4.14)

Para 5, Chromatographic system

Change **to**: Chromatographic system

- a column 25 cm x 4 mm, packed with anion-exchange resin and a 5 cm x 4 mm anion-exchange guard column, both containing ethylvinylbenzene cross linked with 55 per cent divinylbenzene with latex coating of microbeads bonded with alkanol quaternary ammonium ions (6 per cent),
- mobile phase. a 3.0 mM sodium carbonate solution,
- flow rate. 2.0 ml per minute,
- conductivity detector,
- injection volume. 25 µl.

Escitalopram Oxalate. Page 1293

Assay. Chromatographic system, line 7

Change **from**: in 0.1 per cent triethylamine **to**: in 1000 ml of 0.1 per cent triethylamine

Escitalopram Tablets. Page 1294

Dissolution. Line 2

Change **from**: water **to**: 0.1 M hydrochloric acid

Fentanyl Injection. Page 1340

Related substances. *Test solution,* lines 1 and 2

Change **to**: dilute a volume of injection containing about 0.5mg of Fentanyl to 10.0 ml with the mobile phase, if necessary.

Assay. *Test solution*, lines 1 and 2

Change **to**: dilute a volume of injection containing about 0.5mg of Fentanyl to 10.0 ml with the mobile phase, if necessary.

Para 4, line 3

Change **from**: is not less than 2.0 **to**: is not more than 2.0 per cent.

Finasteride Tablets. Page 1351

Related Substances.

Reference Solution (a), lines 2, 3

Change **from**: Diluted 1.0 ml of this solution to 10.0 with the solvent mixture. **to**: Diluted 5.0 ml of this solution to 50.0 with the solvent mixture.

Uniformity of content. *Test solution*, line 1

Change **from**: 25 ml **to**: 2.5 ml

Fluconazole. Page 1353

Related substances. Last para, line 14

Change **from**: other **to**: all the

Folic Acid. Page 1384

Related substances. Reference solution (d), line 5

Change **from**: 10.0 ml **to**: 100.0ml

Free amines. Delete the requirement

Formoterol Fumarate and Budesonide Powder for Inhalation. Page 1387

Assay. *Test solution*

Change **from**: *Test solution*. To a suitable number of intact capsules add 10 ml of *water* and disperse with the aid of ultrasound till the shells get disintegrated. Add 60 ml of the mobile phase and mix further with the aid of ultrasound for 10 minutes with intermittent shaking. Add sufficient of the mobile phase to produce 100.0 ml. Dilute suitably with the mobile phase, if required, to get a final concentration of 0.6 µg per ml of Formoterol Fumarate in the mobile phase. **to**: *Test solution*. Dissolve a quantity of the mixed contents of 20 capsules in sufficient of the mobile phase to get a solution containing 0.6 µg of Formoterol Fumarate per ml.

Gefitinib. Page.1405

Change the **Assay to**:

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 10 mg of the substance under examination in 100 ml of *methanol*.

Reference solution. A 0.01 per cent w/v solution of *gefitinib RS* in the *methanol*.

Chromatographic system as described under Related substances.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of C₂₂H₂₄O₃N₄FCl.

Glibenclamide. Page 1414

Identification. C, line 1

Change **from**: spot **to**: peak

Line 3

Change **from**: with reference solution (a). **to**: with the reference solution.

Related substances. *Reference solution*.

Change **from**: *Reference solution*. Dilute 2.0 ml of the test solution to 100 ml with *methanol*. **to**: *Reference solution*. A 0.00125 per cent w/v solution of *glibenclamide RS* in *methanol*.

Gliclazide. Page 1416

Heavy metals. Line 1

Change **from:** 1.5 g **to:** 2.0 g

Glimepiride. Page 1418

Impurity A. Chromatographic system, line 2

Change **from:** silica gel **to:** diol silica gel

Water

Change **to: Water** (2.3.43). Not more than 0.5 per cent, Method 3, determined by dissolving 0.25 g in 5.0 ml of *dimethylformamide*. Carry out the test on 1.0 ml of solution. Carry out a blank test.

Glimepiride Tablets. Page 1419

Dissolution. Line 7

Change **from:** 15 minutes **to:** 30 minutes

Change the **Related substances to:**

Related substances. Determine by liquid chromatography (2.4.14).

NOTE— Store the solutions at a temperature not exceeding 12° and for not more than 15 hours.

Solvent mixture. 20 volumes of *water* and 80 volumes of *acetonitrile*.

Test solution. Disperse a quantity of powdered tablets containing about 5 mg of Glimepiride in 25.0 ml of the solvent mixture.

Reference solution (a). Dissolve the contents of a vial of *glimepiride for system suitability RS* (containing glimepiride impurity B, C and D) in 2.0 ml of the test solution.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture. Dilute 1.0 ml of this solution to 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.0 mm, packed with endcapped octadecylsilane bonded to porous silica (4 µm),
- mobile phase: a mixture of 50 volumes of a solution prepared by dissolving 0.5 g of *sodium dihydrogen orthophosphate* in 500 ml of *water*, adjusted to pH 2.5 with *orthophosphoric acid* and 50 volumes of *acetonitrile*,
- flow rate. 1 ml per minute,
- spectrophotometer set at 228 nm,
- injection volume. 20 µl.

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to glimepiride impurity B and glimepiride impurity C is not less than 4.0. The relative retention time with reference to glimepiride for 3-ethyl-4-methyl-2-oxo-*N*-[2-(4-sulphamoylphenyl)ethyl]-2,3-dihydro-1*H*-pyrrole-1-carboxamide (glimepiride sulphonamide) (glimepiride impurity B) is about 0.2, for methyl [[4-[2-[[3-(ethyl-4-methyl-2-oxo-2, 3-dihydro-1*H*-pyrrol-1-yl)carbonyl]amino]ethyl]phenyl] sulphonyl]carbamate (glimepiride urethane) (glimepiride impurity C) is about 0.3 and for 1-[[3-[2-[[3-(ethyl-4-methyl-2-oxo-2,3-dihydro-1*H*-pyrrol-1-1)carbonyl]amino]ethyl]n phenyl] sulphonyl]-3-(*trans*-4-methylcyclohexyl)urea (glimepiride impurity D) is about 1.1.

Inject reference solution (a), (b) and the test solution. Run the chromatogram 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of the peak due to glimepiride impurity B is not more than 25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent). The area of any other secondary peak is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). The sum of all the secondary peaks other than glimepiride impurity B is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). The sum of all the secondary peaks is not more than 35 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.5 per cent).

Uniformity of content. *Test solution*, line 1

Change **from:** 100 ml **to:** 10 ml

Guaiphenesin. Page 1430

Identification. B

Change **to**: When examined in the range 200 nm to 400 nm (2.4.7). A 0.004 per cent w/v solution in *methanol* shows absorption maximum as obtained with the *guaiphenesin RS*.

Related substances. Reference solution (b). Line 2

Change **from**: 5.0 ml **to**: 0.5 ml

Reference solution (c). Lines 2 and 3

Change **from**: Dilute 5.0 ml of this solution to 50.0 ml with *acetonitrile*. **to**: Dilute 5.0 ml of this solution to 10.0 ml with the test solution.

Last para, line 1

Change **from**: Inject the test solution and the reference solution. **to**: Inject the test solution, reference solutions (a) and (b).

Line 7

Change **from**: not more than **to**: not more than twice

Heparin Sodium. Page 1439

Para 2, lines 5 to 7

Delete: "and not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of heparin sodium"

Nitrogen. Line 1

Change **from**: 1.3 to 2.5 per cent **to**: Not more than 2.5 per cent

Assay. After para 7

Change **from**: $x_s = x_i + (y_i - 0.5)(x_{i+1} - x_i) / (y_i - y_{i+1})$

to: $x_s = x_i + (y_i - 0.5)(x_{i+1} - x_i) / (y_i - y_{i+1})$

Change **from**: $M = x_s x_u + \log R$

to: $M = x_s - x_u + \log R$

Hyoscine Butylbromide Injection. Page 1467

Change **Assay to**:

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of injection containing about 40 mg of Hyoscine Butylbromide in 100.0 ml of 0.001 M *hydrochloric acid*.

Reference solution. A 0.04 per cent w/v solution of *hyoscine butylbromide RS* in 0.001 M *hydrochloric acid*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (10 µm) (such as Lichrosorb C8),
- mobile phase: a buffer solution prepared by dissolving 2.0 g of *sodium dodecyl sulphate* in mixture of 370 volumes of 0.001 M *hydrochloric acid* and 680 volumes of *methanol*,
- flow rate. 2 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume. 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, tailing factor is not more than 2.0 per cent and the relative standard deviation for replicate injections is not more than 2.0.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{30}BrNO_4$ in the injection.

Hyoscine Butylbromide Tablets. Page 1468

Change **Uniformity of content to**:

Uniformity of content. Comply with the test stated under Tablets.

Determine by liquid chromatography (2.4.14), as described under Assay using following test solution.

Test solution. Disperse one intact tablet in 25.0 ml of 0.001 M *hydrochloric acid*, sonicate for 15 minutes and filter.

Change **Assay to:**

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing about 40 mg of Hyoscine Butylbromide in 60 ml of 0.001 M *hydrochloric acid*, sonicate for 15 minutes, dilute to 100 ml with 0.001 M *hydrochloric acid*, centrifuge and filter.

Reference solution. A 0.04 per cent w/v of solution of *hyoscine butylbromide RS* in 0.001 M *hydrochloric acid*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (10 µm) (such as Lichrosorb C8),
- mobile phase: a buffer solution prepared by dissolving 2.0 g of *sodium dodecyl sulphate* in mixture of 370 volumes of 0.001 M *hydrochloric acid* and 680 volumes of *methanol*,
- flow rate. 2 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume. 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, tailing factor is not more than 2.0 per cent and the relative standard deviation for replicate injections is not more than 2.0.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{30}BrNO_4$ in the tablets.

Imipenem. Page 1486

Related substances. *Solvent mixture*, line 2

Change **from:** 1.35 per cent **to:** 0.0135 per cent

Imipenem and Cilastatin Injection. Page 1487

Labelling.

Change **to:** The label states that the constituted solution should be solubilized in a suitable parenteral fluid prior to intravenous infusion.

Irinotecan Hydrochloride Trihydrate. Page 1508

Microbial contamination. Line 1

Change **from:** Total aerobic microbial count **to:** Total viable aerobic count

Irinotecan Injection. Page 1510

Related substances. *Reference solution (c)*, lines 4-5

Change **from:** solvent mixture **to:** mobile phase

Isoniazid. Page 1515

Hydrazine. Last para, lines 5 and 6

Change **from:** *dimethylaminobenzaldehyde reagent* **to:** *dimethylaminobenzaldehyde solution*

Ketamine Injection. Page 1539

Related substances. Last para, lines 7 and 8

Change **from:** the area of one such peak is not more than **to:** the area of not more than one such peak is more than

Ketoconazole. Page 1540

Identification.

Delete "Test B"

Line 8

Change **from:** C **to:** B

Lactulose. Page 1555

Methanol. Line 1

Delete " Not more than 20 ppm."

Lead. Change **to:**

Lead. Not more than 0.5 ppm.

Determine by atomic absorption spectrometry (2.4.2).

Solvent mixture. Equal volumes of *dilute acetic acid* and *water*.

Test solution. Dissolve 20.0 g of the substance under examination in 100 ml of the solvent mixture. Add 2.0 ml of 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (a). Dissolve 0.5 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (b). Dissolve 1.0 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (c). Dissolve 1.5 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Set the zero of the instrument using *methyl isobutyl ketone* treated as described for the test solution without the substance under examination. Measure the absorbance at 283.3 nm using a lead hollow-cathode lamp as source of radiation and an air-acetylene flame.

Lamivudine, Nevirapine and Stavudine Tablets. Page 1564

Dissolution. Medium

Change **from:** 0.01 M hydrochloric acid **to:** 0.1 M hydrochloric acid

Linezolid Tablets. Page 1591

Related substances. Chromatographic system, Mobile phase B., line 1

Change **from:** 90 volumes **to:** 10 volumes

Lisinopril. Page 1593

Specific optical rotation.

Change **to:** - 43.0 to - 47.0, determined on 1.0 per cent w/v solution in *zinc acetate solution*.

Lopinavir. Page 1602

Related substances, para 2 and 3

Change **from**: *Test solution*. Dissolve 0.1 g of the substance under examination in 100 ml of solvent mixture.

Reference solution. A 0.01 per cent w/v solution of *lopinavir RS* in solvent mixture.

to: *Test solution*. Dissolve 15 mg of the substance under examination in 100 ml of the solvent mixture.

Reference solution. A 0.015 per cent w/v solution of *lopinavir RS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Last para

Change **from**: Inject separately the test solution and the reference solution. Any secondary peak should not be more than 0.3 per cent and the sum of the areas of all the secondary peaks should not be more than 1.0 per cent when calculated by percentage area normalisation. **to**: Inject the test solution and the reference solution. In the chromatogram obtained with the test solution the area of any secondary peak is not more than 0.3 times the area of the peak in the chromatogram obtained with the reference solution (0.3 per cent) and sum of the areas of all the secondary peaks is not more than the area of the peak in the chromatogram obtained with the reference solution (1.0 per cent).

Light Magnesium Oxide. Page 1624

Appearance of solution. Last line

Change **from**: BS2 (2.3.1) **to**: BS2 (2.4.1)

Magnesium Stearate. Page 1625

Fatty acid composition. Chromatographic system, line 1

Change **from**: a stainless steel column **to**: a capillary column

Mannitol. Page 1633

Sulphates, line 1

Change **from**: 10 ml of *water* **to**: 15 ml of *water*

Metformin Hydrochloride. Page 1657

Assay. Line 2

Change **from**: *acetic anhydride* **to**: *acetonitrile*

Line 5

Change **from**: 0.008281 g **to**: 0.01656 g

Metronidazole Benzoate Oral Suspension. Page 1684

Usual strength.

Change **from**: **Usual strength**. 4 mg per ml; 5 mg per ml **to**: **Usual strengths**. 40 mg per ml; 50 mg per ml

Monothioglycerol. Page 1703

Refractive index.

Change **from**: 1.521 to 1.526 **to**: 1.521 to 1.526 at 25°

Montelukast Tablets. Page 1705

Para 1, line 3

Change **from**: C₃₅H₃₅ClNO₃S **to**: C₃₅H₃₆ClNO₃S

Dissolution. *Reference solution* Change **to**:

Reference solution. Dissolve a quantity of *montelukast sodium RS* in the dissolution medium and dilute with dissolution medium to obtain a solution having a known concentration similar to the test solution.

Last line

Change **from**: C₃₅H₃₅ClNO₃S **to**: C₃₅H₃₆ClNO₃S

Assay. Chromatographic system line 10

Change **from**: 345 nm **to**: 240 nm

Last line

Change **from**: C₃₅H₃₅ClNO₃S **to**: C₃₅H₃₆ClNO₃S

Mycophenolate Mofetil. Page 1719

Related substances. Chromatographic system, line 6

Change **from:** 2 volumes **to:** 0.2 volume

Nandrolone Decanoate. Page 1750

Storage. Line 1

Change **from:** Store protected from light and moisture **to:** Store protected from light and moisture, at a temperature between 2° to 8°.

Neomycin Sulphate. Page 1763

Line 4

Change **from:** 600 Units **to:** 680 Units

Nifedipine Tablets. Page 1782

Line 3

Delete “The tablets may be coated”

Ondansetron Oral Solution. Page 1818

Identification. A, line 2

Change **from:** *silica gel G.* **to:** *silica gel GF254.*

Related substances. *Test solution*

Change **from:** *Test solution.* Weigh accurately a quantity of oral solution containing about 45 mg of Ondansetron Hydrochloride in 50-ml volumetric flask, dissolve and dilute with the mobile phase and mix. Dilute 5.0 ml of this solution to 50 ml with the mobile phase. **to:** *Test solution.* Weigh accurately a quantity of oral solution containing about 4.5 mg of Ondansetron Hydrochloride in 50-ml volumetric flask, dissolve and dilute with the mobile phase and mix.

Storage.

Change **from:** Store protected from light and moisture. **to:** Store protected from light, at a temperature not exceeding 30°.

Ondansetron Orally Disintegrating Tablets. Page 1816

Water. Delete the requirement

Ondansetron Oral Solution. Page 1818

Related substances. Para 3, last sentence

Change **from:** The relative retention time with reference to ondansetron for ondansetron impurity A is about 1.1. **to:** The relative retention time with reference to ondansetron for ondansetron impurity D is about 0.34, for imidazole is about 0.4, for 2-methyl imidazole is about 0.53, for des-C-methyl ondansetron hydrochloride is about 0.62, for N-Desmethyl ondansetron maleate is about 0.83, for ondansetron impurity A is about 1.2.

Oxazepam. Page 1830

Related substances. *Reference solution (d).* Line 1

Change **from:** solution (d) **to:** reference solution (c)

Oxytocin Injection. Page 1845

Line 3

Change **from:** 95.0 per cent **to:** 90.0 per cent

Line 4

Change **from:** 105.0 per cent **to:** 110.0 per cent

Pantoprazole Sodium. Page 1856

Related substances. Last para

Change to: Inject the test solution and the reference solution. In the chromatogram obtained with the test solution the area of the peak due to pantoprazole impurity C determined at wavelength 305 nm at relative retention time about 0.6 is not more than 0.077 times the area of the principal peak at 290 nm in the chromatogram obtained with the reference solution (0.5 per cent), the area of any other secondary peak is not more than 0.077 times the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 0.15 times the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent).

Storage. Line 1 and 2

Change from: Store protected from light and moisture, between 2° to 8°. **to:** Store protected from light and moisture, at a temperature not exceeding 30°.

Paracetamol. Page 1859

4-Aminophenol. Delete the test

Related substances. After chromatographic system, para 1 and 2

Change to: Inject reference solution (c). The test is not valid unless the resolution between the peaks due to 4-aminophenol and paracetamol is not less than 4.0 and the signal-to-noise ratio of the peak due to chloroacetanilide is not less than 50. The relative retention time with reference to paracetamol for 4-aminophenol is about 0.8, for 4-nitrophenol is about 3.0 and for chloroacetanilide is about 7.0.

Inject the test solution, reference solution (a), (b), (c) and (d). Run the chromatogram 12 times the retention time of the principal peak. In the chromatogram obtained with the test solution the area of the peak due to chloroacetanilide is not more than 0.2 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (10 ppm) and the area of the peak due to 4-aminophenol is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (50 ppm). The area of the peak due to 4-nitrophenol is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent). The area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent). The sum of the areas of other secondary peaks is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Paracetamol Tablets. Page 1861

4-Aminophenol. Delete the test

Pethidine. Page 1883

Related substances.

Change to: Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 20 volumes of *acetonitrile* and 80 volumes of *water*.

Test solution (a). Dissolve about 0.1 g of the substance under examination in 25.0 ml of the solvent mixture.

Test solution (b). Dissolve about 0.125 g of the substance under examination in 10.0 ml of the solvent mixture.

Reference solution (a). Dilute 0.5 ml of test solution (a) to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *1-methyl-4-phenylpiperidine RS (pethidine impurity A RS)* to 100.0 ml with the solvent mixture.

Reference solution (c). Dissolve 12.5 mg of *1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine* in 10.0 ml of the solvent mixture. Dilute 1.0 ml of this solution to 100.0 ml with the solvent mixture.

Reference solution (d). Dilute 5.0 ml of reference solution (b) and 1.0 ml of reference solution (c) to 100.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.0 mm packed with endcapped octadecylsilane bonded to porous silica (5 µm) (Such as Inertsil ODS2),

- mobile phase: A. a mixture of equal volumes of 4.2 per cent w/v solution of *sodium perchlorate* and 1.2 per cent v/v solution of *orthophosphoric acid*, adjusted to pH 2.0 with *triethylamine*,
B. *acetonitrile*,
- a linear gradient programme using the conditions given below,
- flow rate. 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume. 50 µl.

Time (min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0 – 15	80 → 75	20 → 25
15 – 31	75 → 55	25 → 45
31 – 40	55	45
40 – 41	55 → 80	45 → 20
41 – 50	80	20

Inject reference solution (c). The test is not valid unless the signal-to-noise ratio for the first peak is not less than 10 and peak-to-valley ratio where H_p is height above the baseline, and H_v is height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A is not less than 4.0. The relative retention time with reference to pethidine for pethidine impurity B is about 0.66 and for pethidine impurity A is about 0.68.

Inject test solution (a), (b), reference solution (a) and (d). In the chromatogram obtained with test solution (b), the area of the peak due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (pethidine impurity B) is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (10 ppm). In the chromatogram obtained with test solution (a), the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Phenoxyethanol. Page 1895

Para 1, lines 2 and 3

Delete: “calculated on the dried basis.”

Identification

Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *phenoxyethanol RS*.

B. When examined in the range 240 nm to 350 nm (2.4.7), a 0.008 per cent w/v solution in *water*, shows two absorption maxima at 269 nm and 275 nm and specific absorbance at 269 nm is 95 to 105 and at 275 nm is 75 to 85.

C. Shake 2 ml of Phenoxyethanol with a mixture of 4.0 g of *potassium permanganate*, 5.4 g of *sodium carbonate* and 75 ml of *water* for 30 minutes. Add 25 g of *sodium chloride* and stir continuously for 60 minutes, filter and adjusted to pH 1.7 with *hydrochloric acid*. The melting point of the precipitate, after recrystallisation from *water* is 96° to 99°.

Related substances

Change **to**: Determine by Gas chromatography (2.4.13).

Internal standard solution. Dissolve 1.25 g of *methyl laurate* in 25.0 ml of *dichloromethane*.

Test solution (a). Dissolve 5 g of the substance under examination in 10.0 ml of *dichloromethane*.

Test solution (b). Dissolve 5 g of the substance under examination in 10.0 ml of *dichloromethane* and add 1.0 ml of the internal standard solution.

Reference solution. Add 10.0 ml of the internal standard solution to 1.0 ml of test solution (a) and dilute to 100.0 ml with *dichloromethane*.

Chromatographic system

- a glass column 1.5 m x 4 mm, packed with silanised diatomaceous earth support (150 to 180 mesh) coated with 3 per cent w/w solution of polymethylphenyl-siloxane,
- temperature:
column. 130°,
inlet port and detector at 200°,
- flame ionization detector,
- flow rate. 30 ml per minute using nitrogen as a carrier gas.

Inject 1 µl of the reference solution. The test is not valid unless the resolution between the peaks due to phenoxyethanol and methyl laurate is not less than 12.

Inject 1 µl of test solution (b) and the reference solution. In the chromatogram obtained with test solution (b), the ratio of the area of the peak due to phenoxyethanol to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with test solution (b), the ratio of the area of the sum of any secondary peak and the peak due to the internal standard is not more than 1.0 per cent.

Phenol.

Change **to**: Not more than 0.1 per cent.

Dissolve 1.0 g in 50 ml of *dichloromethane* with 1 ml of dilute *sodium hydroxide solution* and 10 ml of *water*. Wash the upper layer with 2 quantities, each of 20 ml of *dichloromethane* and dilute to 100.0 ml with *water*. The absorbance at the maxima at 287 nm (2.4.7) is not more than 0.27.

Phenytoin Capsules. Page 1906

Usual strength.

Change **from**: **Usual strength.** 10 mg **to**: **Usual strengths.** 25 mg, 50 mg and 100 mg

Pioglitazone Tablets. Page 1917

Assay. *Reference solution*, line 1

Change **from**: 0.015 per cent **to**: 0.0136 per cent

Piperacillin. Page 1918

Appearance of solution. Lines 1 and 2

Change **from**: *carbon dioxide-free water* **to**: *sodium carbonate solution*

Piroxicam. Page 1926

Related substances. After chromatographic system, para 1 and 2

Change **to**: Inject the reference solution. The test is not valid unless the column efficiency is not less than 5000 theoretical plates; tailing factor is not more than 2.0 per cent. The relative standard deviation for replicate injections is not more than 2.0 per cent. The relative retention time with reference to piroxicam for piroxicam impurity B is about 0.85.

Inject the test solution and the reference solution. Run the chromatogram 5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent), the sum of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (0.4 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.02 per cent).

Prednisolone Sodium Phosphate. Page 1955

Para 1, line 3

Change **from**: on the dried basis. **to**: on the anhydrous basis.

Pregabalin. Page 1960

Enantiomeric purity. Para 1

Change **from**: *Marfey's reagent*. Dissolve about 0.1502 g of marfey's reagent in 50 ml of *acetone*. **to**: *Marfey's reagent*. Dissolve about 0.1502 g of marfey's reagent in 50 ml of *acetone*.

Pregabalin Capsules. Page 1961

Related substances. *Test solution.*

Change **from:** *Test solution.* Mix the content of 10 capsules. Weigh and disperse a quantity containing about 15 mg of Pregabalin, in about 25 ml of the solvent mixture, sonicate for 30 minutes and dilute to 100.0 ml with the solvent mixture. **to:** *Test solution.* Weigh and disperse a quantity containing about 750 mg of Pregabalin, in about 25 ml of the solvent mixture, sonicate for 30 minutes and dilute to 50.0 ml with the solvent mixture.

Last para, line 1

Change **from:** Inject reference solution (a) and the test solution. **to:** Inject reference solutions (a), (c) and the test solution.

Propofol. Page 1985

Related substances. Last para, line 4

Change **from:** propofol impurity G **to:** propofol impurity G, multiplied with relative response factor 5.0
Line 7

Change **from:** propofol impurity E **to:** propofol impurity E, multiplied with relative response factor 0.25

Quetiapine Tablets. Page 2014

Para 1, line 3

Change **from:** C₂₁H₂₅N₃O₂S **to:** C₄₂H₅₀N₆O₄S₂

Assay. Last line

Change **from:** C₂₁H₂₅N₃O₂S **to:** C₄₂H₅₀N₆O₄S₂

Rabeprazole Tablets. Page 2037

Change **Dissolution to:**

Dissolution (2.5.2).

A. Apparatus No. 1,

Medium. 900 ml of *0.1 M hydrochloric acid*,

Speed and time. 50 rpm and 120 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtered solution immediately, suitably diluted with the dissolution medium, if necessary, at the maximum at about 291 nm (2.4.7). Calculate the content of C₁₈H₂₀N₃O₃SNa in the medium from the absorbance obtained from a solution of known concentration of *rabeprazole sodium RS*, prepared by dissolving in minimum quantity of a mixture of 75 volumes of *acetonitrile* and 25 volumes of *methanol* and suitably diluted with the dissolution medium.

D. Not less than 10 per cent of the stated amount of C₁₈H₂₀N₃O₃SNa.

B. Apparatus No. 1,

Medium. 900 ml of *phosphate buffer pH 7.4* prepared by dissolving 5.8 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 7.4 with *sodium hydroxide solution*.

Speed and time. 75 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtered solution immediately, suitably diluted with the dissolution medium, if necessary, at the maximum at about 291 nm (2.4.7). Calculate the content of C₁₈H₂₀N₃O₃SNa in the medium from the absorbance obtained from a solution of known concentration of *rabeprazole sodium RS*, prepared by dissolving in minimum quantity of a mixture of 75 volumes of *acetonitrile* and 25 volumes of *methanol* and suitably diluted with the dissolution medium.

D. Not less than 70 per cent of the stated amount of C₁₈H₂₀N₃O₃SNa.

Serratiopeptidase. Page 2097

Identification. Line 4

Change **from:** 0.04 ml **to:** 0.04 M

Microbial contamination. Lines 2 and 3

Change **from:** 1 ml **to:** 1 g

Assay. Line 2

Change **from:** 1 µm **to:** 1 µg

Protein precipitating solution, line 3
Change **from**: 100 ml **to**: 1000 ml

Reference tyrosine curve. Line 5
Change **from**: *sodium carbonate solution* **to**: 6.0 per cent w/v *sodium carbonate solution*

Test solution. Line 7
Change **from**: 0.6 per cent **to**: 6.0 per cent

Blank solution, line 6
Change **from**: 50 ml of 0.6 per cent **to**: 5 ml of 6.0 per cent

Sildenafil Tablets. Page 2101

Para 1, lines 2 and 3
Change **from**: sildenafil citrate, $C_{28}H_{38}N_6O_{11}S$. **to**: sildenafil, $C_{22}H_{30}N_6O_4S$.

Dissolution. Lines 7 and 11
Change **from**: $C_{28}H_{38}N_6O_{11}S$ **to**: $C_{22}H_{30}N_6O_4S$

Assay. Last line
Change **from**: $C_{28}H_{38}N_6O_{11}S$ **to**: $C_{22}H_{30}N_6O_4S$

Simvastatin Tablets. Page 2104

Dissolution. Line 13
Change **from**: minimum at about 257 nm **to**: minimum at about 247 nm

Assay. *Test solution.*

Change **from**: *Test solution.* Disperse a quantity of whole tablets containing about 0.16 g of Simvastatin in *water* and mix with the aid of ultrasound and shaking. Add sufficient of solution A to produce about 75 ml, mix with the aid of ultrasound and shaking for 15 minutes, dilute to 100 ml with solution A and centrifuge. Dilute 1 ml of the clear supernatant solution with sufficient of solution A to produce a solution containing 0.01 per cent w/v of Simvastatin. **to**: *Test solution.* Weigh and powder 20 tablets. Weigh a quantity of the powder containing about 100 mg of Simvastatin, disperse in 100 ml of solution A and filter. Dilute 5.0 ml of the solution to 50.0 ml with solution A.

Salbutamol. Page 2083

Identification. C

Change **to**: In the test for Related substances, the principal peak in the chromatogram obtained with the test solution corresponds to the peak due to salbutamol that in the chromatogram obtained with the reference solution.

Related substances. *Reference solution,* line 1
Change **from**: 0.02 per cent **to**: 0.03 per cent

Salbutamol Sulphate. Page 2085

Identification. C

Change **to**: In the test for Related substances, the principal peak in the chromatogram obtained with the test solution corresponds to the peak due to salbutamol that in the chromatogram obtained with the reference solution.

Related substances. *Reference solution,* line 1
Change **from**: 0.02 per cent **to**: 0.03 per cent

Simvastatin. Page 2103

Assay. After chromatographic system, line 3
Change **from**: not less than 5.0. **to**: not less than 4.0.

Sodium Fusidate. Page 2123

Identification. B

Test B: Delete the test

Test C

Change from: to: B.

Sodium Methylparaben. Page 2132

Identification. B

Change to: A 5 per cent w/v solution gives the reactions of sodium salts (2.3.1).

Sorbitol Solution (70 Per cent)

(Crystallising) Monograph change to:

Sorbitol Solution (70 Per cent) (Crystallising)

Sorbitol (70 per cent) (Crystallising)

Sorbitol Solution (70 per cent) (Crystallising) is an aqueous solution of hydrogenated, partly hydrolysed starch.

Sorbitol Solution (70 per cent) (Crystallising) contains not less than 68.0 per cent m/m and not more than 72.0 per cent m/m of anhydrous substances and not less than 92.0 per cent w/w and not more than 101.0 per cent w/w of D-glucitol, $C_6H_{14}O_6$), calculated on the anhydrous basis.

Category. Pharmaceutical aid.

Description. A clear, colourless, syrupy liquid, miscible with water.

Identification

A. In the Assay, the principle peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

B. To 7.0 g, add 40 ml of *water* and 6.4 g of *disodium tetraborate*. Allow to stand for 1 hour, shake occasionally and dilute to 50.0 ml with *water*. The angle of rotation (2.4.22) is $+0^\circ$ to $+1.5^\circ$.

C. It is clear syrupy liquid at 25° .

Tests

Appearance of solution. A 14.0 per cent w/v solution in *water* is clear (2.4.1), and colourless (2.4.1).

Conductivity (2.4.9). Not more than $10 \mu\text{S cm}^{-1}$, measured on undiluted liquid sorbitol (crystallizing) while gently stirring with a magnetic stirrer.

Reducing sugars. Not more than 0.2 per cent, calculated as glucose equivalent.

To 5.0 g add 6.0 ml of *water*, 20.0 ml of *cupri-citric solution* and a few glass beads. Heat so that boiling begins after 4 minutes and maintain boiling for 3 minutes. Cool rapidly and add 100.0 ml of a 2.4 per cent v/v solution of *glacial acetic acid* and 20.0 ml of *0.025 M iodine*. With continuous shaking, add 25.0 ml of a mixture of 6 volumes of *hydrochloric acid* and 94 volumes of *water* and when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulphate* using 1 ml of *starch solution*, added towards the end of the titration, as indicator. Not less than 12.8 ml of *0.05 M sodium thiosulphate* is required.

Lead. Not more than 0.5 ppm.

Determine by atomic absorption spectrometry (2.4.2), Method A.

Solvent mixture. Equal volumes of *dilute acetic acid* and *water*.

Test solution. Dissolve 20.0 g of the substance under examination in 100 ml of the solvent mixture. Add 2.0 ml of 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (a). Dissolve 0.5 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (b). Dissolve 1.0 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (c). Dissolve 1.5 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Set the zero of the instrument using *methyl isobutyl ketone* treated as described for the test solution without the substance under examination. Measure the absorbance at 283.3 nm using a lead hollow-cathode lamp as source of radiation and an air-acetylene flame.

Nickel. Dissolve 10.0 g in sufficient *water* to produce 20 ml, add 3.0 ml of *bromine water* and 2.0 ml of a 20 per cent w/v solution of *citric acid*, mix and add 10.0 ml of 6 M *ammonia* and 1.0 ml of a 1.0 per cent w/v solution of *dimethylglyoxime* in *ethanol (95 per cent)*. Mix, dilute to 50.0 ml with *water* and allow to stand for 5 minutes; any colour produced is not more intense than that produced by treating in the same manner and at the same time 1.0 ml of *nickel standard solution (10 ppm Ni)* diluted to 20.0 ml with *water* (1 ppm).

Water (2.3.43). 28.0 per cent to 32.0 per cent, determined on 0.1 g.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 1.0 g of the substance under examination in 50.0 ml of *water*.

Reference solution (a). Dissolve 65 mg of *sorbitol RS* in 5.0 ml of *water*.

Reference solution (b). Dissolve 65 mg of *mannitol* and 65 mg of *sorbitol* in 5.0 ml of *water*.

Chromatographic system

- a stainless steel column 30 cm x 7.8 mm, packed with strong cation exchange resin (calcium form) (9 µm),
- column temperature. 85°,
- mobile phase: *water*,
- flow rate. 0.5 ml per minute,
- refractometer set at a constant temperature,
- injection volume. 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to sorbitol and mannitol is not less than 2.0. The relative retention time with reference to sorbitol (Retention time is about 27 minutes) for mannitol is about 0.8.

Inject the test solution and reference solution (a). Run the chromatogram for three times the retention time of sorbitol.

Calculate the content of D-sorbitol, C₆H₁₄O₆.

Storage. Store protected from moisture.

Sorbitol Solution (70 Per cent)

(Non-Crystallising) Monograph change to:

Sorbitol Solution (70 Per cent)

(Non-Crystallising)

Sorbitol (70 per cent) (Non-crystallising)

Sorbitol Solution (70 per cent) (Non-crystallising) is an aqueous solution of hydrogenated, partly hydrolysed starch.

Sorbitol Solution (70 per cent) (Non-crystallising) contains not less than 68.0 per cent m/m and not more than 72.0 per cent m/m of anhydrous substances and not less than 72.0 per cent w/w and not more than 92.0 per cent w/w of D-glucitol, C₆H₁₄O₆, calculated on the anhydrous basis.

Category. Pharmaceutical aid (sweetening vehicle); humectant.

Description. A clear, colourless or faintly yellow, syrupy liquid.

Identification

A. In the Assay, the principle peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

B. To 7.0 g add 40 ml of *water* and 6.4 g of *disodium tetraborate*. Allow to stand for 1 hour, shake occasionally and dilute to 50.0 ml with *water*. The angle of rotation (2.4.22) is $+1.5^\circ$ to $+3.5^\circ$.

C. It is clear syrupy liquid at 25° .

Tests

Appearance of solution. A 14.0 per cent w/v solution in *water* is clear (2.4.1), and colourless (2.4.1).

Conductivity (2.4.9). Not more than $10 \mu\text{S cm}^{-1}$, measured on undiluted liquid sorbitol while gently stirring with a magnetic stirrer.

Reducing sugars. Not more than 0.2 per cent, calculated as glucose equivalent.

To 5.0 g add 6.0 ml of *water*, 20.0 ml of *cupri-citric solution* and a few glass beads. Heat so that boiling begins after 4 minutes and maintain boiling for 3 minutes. Cool rapidly and add 100.0 ml of a 2.4 per cent v/v solution of *glacial acetic acid* and 20.0 ml of *0.025 M iodine*. With continuous shaking, add 25.0 ml of a mixture of 6 volumes of *hydrochloric acid* and 94 volumes of *water* and when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulphate* using 1 ml of *starch solution*, added towards the end of the titration, as indicator. Not less than 12.8 ml of *0.05 M sodium thiosulphate* is required.

Reducing sugars after hydrolysis. Not more than 9.3 per cent, calculated as glucose equivalent.

To 6.0 g add 35 ml of *water*, 40 ml of *1 M Hydrochloric acid* and a few glass beads. Reflux for 4 hours. Cool and neutralize with *dilute sodium hydroxide solution* using 0.2 ml of *bromothymol blue solution* as indicator. Cool and dilute to 100.0 ml with *water*. To 3.0 ml of the solution add 5.0 ml of *water*, 20 ml of *cupri-citric solution* and a few glass beads. Heat so that boiling begins after 4 minutes and maintain boiling for 3 minutes. Cool rapidly and add 100 ml of a 2.4 per cent v/v solution of *glacial acetic acid* and 20.0 ml of *0.025 M iodine*. With continuous shaking, add 25 ml of a mixture of 6 volumes of *hydrochloric acid* and 94 volumes of *water* and when the precipitate has dissolved, titrate the excess of iodine with *0.05 M sodium thiosulphate* using 1 ml of *starch solution*, added towards the end of the titration, as indicator. Not less than 8.0 ml of *0.05 M sodium thiosulphate* is required.

Lead. Not more than 0.5 ppm.

Determine by atomic absorption spectrometry (2.4.2).

Solvent mixture. Equal volumes of *dilute acetic acid* and *water*.

Test solution. Dissolve 20.0 g of the substance under examination in 100 ml of the solvent mixture. Add 2.0 ml of 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (a). Dissolve 0.5 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (b). Dissolve 1.0 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Reference solution (c). Dissolve 1.5 ml of *lead standard solution (10 ppm Pb)* in 100 ml of solvent mixture. Add 2.0 ml of a clear 1 per cent w/v solution of *ammonium pyrrolidinedithiocarbamate* and 10.0 ml of *methyl isobutyl ketone*, shake for few seconds and protected from bright light. Allow the layers to separate and use the methyl isobutyl ketone layer.

Set the zero of the instrument using *methyl isobutyl ketone* treated as described for the test solution without the substance under examination. Measure the absorbance at 283.3 nm using a lead hollow-cathode lamp as source of radiation and an air-acetylene flame.

Nickel. Dissolve 10.0 g in sufficient *water* to produce 20 ml, add 3.0 ml of *bromine water* and 2.0 ml of a 20 per cent w/v solution of *citric acid*, mix and add 10.0 ml of 6 M *ammonia* and 1.0 ml of a 1.0 per cent w/v solution of *dimethylglyoxime* in *ethanol (95 per cent)*. Mix, dilute to 50.0 ml with *water* and allow to stand for 5 minutes; any colour produced is not more intense than that produced by treating in the same manner and at the same time 1.0 ml of *nickel standard solution (10 ppm Ni)* diluted to 20.0 ml with *water* (1 ppm).

Water (2.3.43). 28.0 per cent to 32.0 per cent, determined on 0.1 g.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 1.0 g of the substance under examination in 50.0 ml of *water*.

Reference solution (a). Dissolve 55 mg of *sorbitol RS* in 5.0 ml of *water*.

Reference solution (b). Dissolve 55 mg of *mannitol* and 55 mg of *sorbitol* in 5.0 ml of *water*.

Chromatographic system

- a stainless steel column 30 cm x 7.8 mm, packed with strong cation exchange resin (calcium form) (9 µm),
- column temperature. 85°,
- mobile phase: *water*,
- flow rate. 0.5 ml per minute,
- refractometer set at a constant temperature,
- injection volume. 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to sorbitol and mannitol is not less than 2.0. The relative retention time with reference to sorbitol (Retention time is about 27 minutes) for mannitol is about 0.8.

Inject the test solution and reference solution (a). Run the chromatogram for three times the retention time of sorbitol.

Calculate the content of D-sorbitol, C₆H₁₄O₆.

Storage. Store protected from moisture.

Stearic Acid. Page 2154

Change **Assay to:**

Assay. Determine by gas chromatography (2.4.13).

Test solution. Dissolve 0.1 g of substance under examination in 5 ml of *boron trifluoride-methanol solution* in a conical flask fitted with a reflux condenser. Reflux for 10 minutes, add 4.0 ml of *heptane* through the condenser and boil again for 10 minutes. Allow to cool, add 20 ml of a saturated solution of *sodium chloride*. Shake and allow the layers to separate. Remove about 2 ml of the organic layer and dry it over 0.2 g of *anhydrous sodium sulphate*. Dilute 1.0 ml of this solution to 10.0 ml with *heptane*.

Reference solution. Dissolve 50 mg of *palmitic acid RS* and 50 mg of *stearic acid RS* in 5 ml of *boron trifluoride-methanol solution* in a conical flask fitted with a reflux condenser. Reflux for 10 minutes, add 4.0 ml of *heptane* through the condenser and boil again for 10 minutes. Allow to cool, add 20 ml of a saturated solution of *sodium chloride*. Shake and allow the layers to separate. Remove about 2 ml of the organic layer and dry it over 0.2 g of *anhydrous sodium sulphate*. Dilute 1.0 ml of this solution to 10.0 ml with *heptane*.

Chromatographic system

- a fused-silica column 30 m x 0.32 mm, packed with macrogol 20000 (0.5 µm),
- temperature:
column 70° from 0 to 2 minutes, 70° - 240° from 2 to 36 minutes and hold at 240° from 36 to 41 minutes,
inlet port at 220° and detector at 260°,
- a flame-ionisation detector,
- flow rate. 2.4 ml per minute using nitrogen as carrier gas.

Inject 1 µl of the reference solution. The test is not valid unless the resolution between the peaks due to methyl palmitate and methyl stearate is not less than 5.0. The relative retention time with reference to methyl stearate for methyl palmitate is about 0.9. The relative standard deviation of methyl stearate and methyl palmitate for replicate injections is not more than 3.0 per cent.

Inject 1 µl of the reference solution and the test solution.

Calculate the content of stearic acid.

Terazosin Hydrochloride. Page 2194

Water. Line 1

Change **from:** 7.8 to 8.6 per cent **to:** 7.0 to 8.6 per cent

Terbutaline Sulphate. Page 2195

Identification. C

Change **to:** In the test for Related substances, the principal peak in the chromatogram obtained with the test solution corresponds to the peak due to terbutaline sulphate that in the chromatogram obtained with reference solution (a).

Related substances. Last para,

Change **to:** Inject the test solution, reference solution (a) and (b). Run the chromatogram 6 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of the peak due to terbutaline impurity C is not more than twice area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of other secondary peaks, for each peak is not more than area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent). The sum of all the secondary peaks other than terbutaline impurity C is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent).

Terbutaline Tablets. Page 2198

Dissolution. Para 1,

Change **to:** Withdraw a suitable volume of the medium and filter. Carry out the method as described under Assay beginning at the words "To 5.0 ml add 35 ml of a buffer solution...". Calculate the content of $(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4$ in the medium from the absorbance obtained from a solution of known concentration of *terbutaline RS* prepared in the same manner.

Tramadol Hydrochloride. Page 2245

Specific optical rotation. Line 1

Change **from:** **Specific optical rotation to: Optical rotation**

Thiocolchicoside. Page 2213

Bacterial endotoxins. Replace the test with the following

Insert the following before **Storage**

Thiocolchicoside intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins complies with the following additional requirement.

Bacterial endotoxins (2.2.3). Not more than 87.5 Endotoxin Unit per mg.

Thiocolchicoside intended for use in the manufacture of parenteral preparations without a further appropriate sterilisation procedure complies with the following additional requirement.

Sterility (2.2.11). Complies with the test for sterility.

Topiramate. Page 2243

Usual strengths

Change **from:** 25 mg and 50 mg **to:** 25 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg

Trimetazidine Hydrochloride. Page 2263

Related substances. Change **to:**

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.2 g of the substance under examination in 50 ml of *water*.

Reference solution. Dilute 2.0 ml of the test solution to 100.0 ml with *water*. Dilute 5.0 ml of this solution to 100.0 ml with *water*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature. 30°,
- mobile phase: A. a mixture of 35.7 volumes of *methanol* and 64.3 volumes of a 0.29 per cent w/v solution of *sodium heptanesulphonate*, adjusted to pH 3.0 with *orthophosphoric acid*,
B. *methanol*,
- a linear gradient programme using the conditions given below,
- flow rate. 1.2 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume. 10 µl.

Time (min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0 - 50	95 → 75	5 → 25
50 - 52	75 → 95	25 → 5

Equilibrate the column for not less than 1 hour with the mobile phase.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent. The relative retention time with reference to trimetazidine for (2,3,4-trimethoxyphenyl)methanol (trimetazidine impurity D) is about 0.2, for 2,3,4-trimethoxybenzaldehyde (trimetazidine impurity C) is about 0.4, for ethyl 4-(2,3,4-trimethoxybenzyl)piperazine-1-carboxylate (trimetazidine impurity H) is about 0.6, for 1-(3,4,5-trimethoxybenzyl)piperazine (trimetazidine impurity A) and *N*-methyltrimetazidine (trimetazidine impurity I) is about 0.9, for 1-(2,4,5-trimethoxybenzyl)piperazine (trimetazidine impurity E) is about 0.95, for 1-(2,4,6-trimethoxybenzyl) piperazine (trimetazidine impurity F) is about 1.4 and for 1,4-bis(2,3,4-trimethoxybenzyl) piperazine (trimetazidine impurity B) is about 1.8.

Inject the test solution and the reference solution. In the chromatogram obtained with the test solution, the area of each peak due to trimetazidine impurity A, B, C, D, E, F, H, I multiplied with correction factor 0.55 for impurity B, 0.37 for impurity C and 0.71 for impurity F is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent). The sum of areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Valsartan. Page 2286

Identification. Insert the following before test A

“Test A may be omitted if tests B and C are carried out. Tests B and C may be omitted if test A is carried out.

Test C

Change **from:** When examined in the range 200 nm to 300 nm (2.4.7), a 0.001 per cent w/v solution in 0.1 M hydrochloric acid exhibits a maximum at about 248 nm. **to:** The light absorption of 5 per cent w/v solution in *methanol* at 420 nm (2.4.7) is not more than 0.02.

Valsartan and Hydrochlorothiazide Tablets. Page 2287

Usual strengths. Line 2

Change **from:** 60 mg **to:** 160 mg

Identification. *Reference solution*

Change **from:** *Reference solution.* A solution containing 0.02 per cent w/v each of *valsartan RS* and *hydrochlorothiazide RS* in *acetone*. **to:** *Reference solution.* A solution equivalent to test concentration of *valsartan RS* and *hydrochlorothiazide RS* in *acetone*.

Vancomycin Hydrochloride. Page 2289

Vancomycin B.

Change **to:** **Vancomycin B.** Determine by liquid chromatography (2.4.14).

NOTE- Use freshly prepared solutions.

Test solution (a). Dissolve 10 mg of the substance under examination in mobile phase A and dilute to 5.0 ml with mobile phase A.

Test solution (b). Dilute 2.0 ml of test solution (a) to 50.0 ml with mobile phase A.

Test solution (c). Dilute 0.5 ml of test solution (b) to 20.0 ml with mobile phase A.

Reference solution. A 0.05 per cent w/v solution of *vancomycin hydrochloride RS* in water. Heat at 65° for 24 hours, allow to cool.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
- mobile phase: A. a mixture of 1 volume of *tetrahydrofuran*, 7 volumes of *acetonitrile* and 92 volumes of buffer solution prepared by diluting 1 ml of *triethylamine* to 500 ml with *water*, adjust the pH to 3.2 with *orthophosphoric acid*,

B. a mixture of 1 volume of *tetrahydrofuran*, 29 volumes of *acetonitrile* and 70 volumes of buffer solution prepared by diluting 1 ml of *triethylamine* to 500 ml with *water*, adjust the pH to 3.2 with *orthophosphoric acid*,
- a linear gradient programme using conditions given below,
- flow rate. 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume. 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0-13	100	0
13-22	100-0	0-100
22-26	0	100

Inject test solution (a), (b), (c) and the reference solution. The test is not valid unless the resolution between the two principal peaks in the chromatogram obtained with the reference solution is not less than 5.0, signal-to-noise ratio for the principal peak in the chromatogram obtained with test solution (c) is not less than 5.0 and the tailing factor for the peak due to vancomycin in the chromatogram obtained with the test solution (b) is not more than 1.6.

Calculate the percentage content of vancomycin B hydrochloride using the following expression:

$$\frac{A_b \times 100}{A_b + \left(\frac{A_t}{25}\right)}$$

A_b = area of the peak due to vancomycin B in the chromatogram obtained with test solution (b);

A_t = sum of the areas of the peaks due to impurities in the chromatogram obtained with test solution (a).

Related substances.

Change to: **Related substances.** Determine by liquid chromatography (2.4.14), as described under Vancomycin B with following modifications.

Inject test solution (a), (b) and (c). In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 4.0 per cent. The sum of areas of all the secondary peaks is not more than 7.0 per cent. Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with test solution (c) (0.1 per cent).

Calculate the percentage content of each impurity using the following expression:

$$\frac{\left(\frac{A_i}{25}\right) \times 100}{A_b + \left(\frac{A_t}{25}\right)}$$

A_i = area of the peak due to an impurity in the chromatogram obtained with test solution (a);

A_b = area of the peak due to vancomycin B in the chromatogram obtained with test solution (b);

A_t = sum of the areas of the peaks due to impurities in the chromatogram obtained with test solution (a).

Verapamil Hydrochloride. Page 2295

Identification. C

Change **to:** In the test for Related substances, the principal peak in the chromatogram obtained with the test solution corresponds to the peak due to verapamil that in the chromatogram obtained with reference solution (a).

Verapamil Tablets. Page 2297

Para 1, line 3

Delete “The tablets may be coated”

Vinblastine Injection. Page 2299

Storage. Lines 1 and 2

Change **from:** Store in sealed containers in a deep freezer (Below -18 °) **to:** Store in sealed containers at a temperature of 2° to 8°.

Vincristine Injection. Page 2302

Storage. Lines 1 and 2

Change **from:** Store in sealed containers in a deep freezer (Below -18 °) **to:** Store in sealed containers at a temperature of 2° to 8°.

Warfarin Sodium Clathrate. Page 2312

Isopropyl alcohol. After chromatographic system, para 1

Change **from:** The column temperature may be varied so that the resolution, R, between propan-1-ol and propanol-2-ol is not less than 2.0, the tailing factor, T, for the propan-2-ol is not less than 2.0 the tailing factor T, for the propan-2-ol peak is not more than 1.5 and the relative standard deviation of the ratio of the area due to the peak of propanol-2-ol to that due to propan-1-ol for five replicate injections of reference solution (b) is not more than 2.0 per cent. **to:** The column temperature may be varied so that the resolution between propan-1-ol and propanol-2-ol is not less than 1.5, the tailing factor for the propan-2-ol is not more than 2.0, the tailing factor for the propan-1-ol is not more than 2.0 and the relative standard deviation of the ratio of the area due to the peak of propanol-2-ol to that due to propan-1-ol for five replicate injections of reference solution (b) is not more than 2.0 per cent.

Water.

Change **from:** Not more than 4.0 per cent, determined on 0.75 g. **to:** Not more than 0.3 per cent, determined on 2.5 g.

Water for Injections in Bulk. Page 2315

Para 2, line 4

Change **from:** 10 micro-organisms per ml **to:** 10 micro-organisms per 100 ml

Xylometazoline Nasal Drops. Page 2323

Line 1

Change **from:** Xylometazoline Hydrochloride Nasal Drops **to:** Xylometazoline Hydrochloride Nasal Drops; Xylometazoline Hydrochloride Nasal Solution

Zinc Stearate. Page 2337

Sulphates. Line 1

Change **from:** 2.5 ml of solution A **to:** Dilute 1 ml of solution A to 50 ml with *water*. Dilute 12.5 ml of this solution to 15 ml with *water*

Zoledronic Acid. Page 2339

Add synonym “Zoledronic Acid Monohydrate”

Lines 1, 2 and 3

Change **to:** C₃H₁₀N₂O₇P₂ · H₂O Mol. Wt. 290.1

Zoledronic Acid is [1-hydroxy-2-(1*H*-imidazol-1-yl)ethylidene]diphosphonic acid, monohydrate.

Loss on drying.

Change **from:** **Loss on drying** (2.4.19). **to:** **Water** (2.3.43).

Veterinary Monographs

Ivermectin Injection. Page 2663

Assay. *Test solution*, line 2

Change **from:** *water* **to:** *methanol*

Reference solution, line 2

Change **from:** *water* **to:** *methanol*