INDIAN PHARMACOPOEIA COMMISSION
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No. T.11013/02/2018-AR&D **Date:** 28.02.2020

To,

1. Drugs Controller General (India)
2. CDSCO Zonal Offices
3. All State Drug Controllers
4. Members of Scientific Body of the IPC
5. Members of Sub-Committees of Scientific Body of the IPC
6. Government Analysts
7. Directors of Drugs Testing Laboratories
8. IDMA/OPPI/BDMA/FSSAI/Small Scale Industry Associations

Subject: Amendment List-04 to IP 2018

The 8th Edition of Indian Pharmacopoeia (IP) 2018 has become effective from 1st January, 2018. Based on scientific inputs, some IP monographs needed up-gradation and accordingly Amendment List - 04 to IP 2018 is issued containing such amendments.

This is for notice and compliance with IP 2018.

(Dr. Jai Prakash)
Secretary-cum-Scientific Director (I/c)

Encl. Amendment List-04 to IP 2018

Amendment List 04 to IP-2018

2.3.13. Heavy Metals. Page 139

Method A

Insert before **Standard solution**

Buffer solution. Dissolve 25 g of *ammonium acetate* in 25 ml of *water*, add 38 ml of *6 M hydrochloric acid*. Adjust, if necessary with *3 M ammonium hydroxide* or *6 M hydrochloric acid* to pH 3.5 and dilute with water to 100 ml and mix.

Procedure

Change **from**: To each of the cylinder containing the standard solution and test solution respectively add 10 ml of freshly prepared *hydrogen sulphide solution*, mix, dilute to 50 ml with *water*, allow to stand for 5 minutes and view downwards over a white surface; the colour produced with the test solution is not more intense than that produced with the standard solution.

to: To each of the cylinder containing the standard solution and the test solution respectively, add 2 ml of buffer solution and 1.2 ml of *thioacetamide reagent*, dilute to 50 ml with *water*, mix, allow to stand for 5 minutes and view downwards over a white surface; the colour produced with the test solution is not more intense than that produced with the standard solution.

Method B

Insert before **Standard solution**.

Buffer solution. Proceed as directed under Method A.

2.3.43. Water. Page 156

Primary standardisation of the reagent, lines 4 and 5

Change **from**: *disodium tartrate*, $C_4H_4O_6Na_2$, $2H_2O$, accurately weighed ----------

to: *disodium tartrate*, $C_4H_4O_6Na_2$, $2H_2O$ or suitable amount of water in appropriate form, accurately weighed------

2.3.46. Assay of Insulins. Page 160

Insert after title

Use Method A or Method B, as appropriate.

Method A

Insert at the end

Method B

Determination by liquid chromatography (2.4.14) as described under Assay of Insulins (2.3.46) Method A, following the conditions as described below**:**

Time (min)	Mobile phase (a) (percent v/v)	Mobile phase (b) (percent v/v)
0-30	42	58
30-44	42-11	58-89
44-50	11	89
50-55	42	58

2.4.26. Solubility. Page 220

Isosorbide Dinitrate, Diluted. Page 236

Delete the requirement

Isosorbide Mononitrate, Diluted. Page 236

Delete the requirement

Methylergometrine Maleate. Page 238

Line 1

Change **from:** Soluble in *ethanol (95 per cent)*

to: Slightly soluble in *ethanol (95 per cent*)

2.7.1. Composition of Polysaccharide Vaccines. Page 333

Phosphorus, Method.

Para 1, line 6

Change **from**: .....4 ml each of *water* and *ammonium molybdate reagent.*

to: .....4 ml each of *water* and *ammonium molybdate reagent* prepared by mixing 1 volume of a 25 g per litre solution of ammonium molybdate, 1 volume of a 100 g per litre solution of ascorbic acid and 1 volume of sulphuric acid (294.5 g per litre) and 2 volume of water.

Protein Content, Method.

Para 1, line 1

Change **from**: Add 2 ml of *cupri-tartaric solution*……..

to: Add 2 ml of *cupri-tartaric solution* prepared by adding 1 ml of solution I containing 10 g per litre of copper sulphate and 20 g per litre of sodium tartrate, to 50 ml of solution II containing 40 g per litre solution of sodium carbonate in 0.2 M sodium hydroxide.

5.9. Reference Substances (IPRS). Page 1018

Insert at the end

Reference standard for vaccines

Considering the inherent variability in biological assays usage of reference standards are necessary at some stage in production of vaccines and antisera for their effective quality control. Since these standards are key materials in establishing quality of products, they have to be properly established, maintained and monitored to ensure efficacy of the vaccines and antisera.

For many vaccines and antisera for human use, National Reference Standards (NRS) are established, maintained and supplied by Central Drugs Laboratory (CDL), Kasauli. NRS are calibrated against the International Reference Standard (IRS) and are supplied to various vaccine and antisera manufacturers across the country. NRS are thus traceable to the IRS supplied by NIBSC, London. To ensure judicious use of NRS and IRS, manufacturers are encouraged to develop their In House Reference Standards in comparison to the NRS and/or IRS.

Lotions. Page 4411

Change **from**: **Uniformity of weight per volume**. Unless otherwise specified, Oral Liquids comply with the test for contents of packaged dosage forms (2.5.6).

to: **Uniformity of weight or volume**. Unless otherwise specified, Lotions comply with the test for contents of packaged dosage forms (2.5.6).

Alprostadil. Page 1182

Related substances

System A. Chromatographic system, gradient programme, line 2

Change **to:**

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
75	100	0

System B. Chromatographic system, gradient programme, line 2

Change **to:**

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
50	100	0

Aluminium, Magnesium and Simethicone Oral Suspension. Page 1188

Labelling. Line 1

Change **from:** may be

to: to be

Aluminium, Magnesium and Simethicone Chewable Tablets. Page 1190

Labelling. Line 3

Change **from:** may be

to: to be

Amiodarone Intravenous Infusion. Page 1212

Insert before **Other tests**

Bacterial endotoxins (2.2.3). Not more than 8.33 Endotoxin Units per mg of amiodarone hydrochloride.

Arteether. Page 1264

Line 1

Change **from:** a-b Arteether

to: α- β Arteether

Benzyl Alcohol. Page 1354

Related substances. *Reference solution (c)*

Line 1

Change **from:** *benzaldehyde*

to: *benzyl alcohol impurity A (benzaldehyde)*

Line 2

Change **from:** *cyclohexylmethanol*

to: *benzyl alcohol impurity B (cyclohexylmethanol)*

Benzyl alcohol not intended for parenteral use

Insert after first para

If any peaks in the chromatogram obtained with the test solution have the same retention time as the peaks due to ethyl benzene or dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms obtained with reference solution (c) or (d) (corrected peak areas of ethyl benzene and dicyclohexyl). Any such peaks in the chromatogram obtained with the test solution are to be included in the assessments for the sum of other peaks.

Benzyl alcohol intended for parenteral use

Insert after first para

If any peaks in the chromatogram obtained with the test solution have the same retention time as the peaks due to ethyl benzene or dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms obtained with reference solution (c) or (d) (corrected peak areas of ethyl benzene and dicyclohexyl). Any such peaks in the chromatogram obtained with the test solution are to be included in the assessments for the sum of other peaks.

Bronopol. Page 1411

Water

Change **from:** Not more than 0.5 per cent, determined on 5.0 g.

to: Not more than 0.5 per cent, determined on 2.0 g.

Bupivacaine Injection. Page 1422

Bacterial endotoxins

Change **from**: Not more than 2.5 Endotoxin Units per mg of bupivacaine.

to: Not more than 2.5 Endotoxin Units per mg of bupivacaine hydrochloride.

Butyl Paraben. Page 1431

Acidity. Line 1

Change **from:** To 2 ml of solution A, add 3 ml of *ethanol*……..

to: To 2 ml of 10 per cent w/v solution in *ethanol (95 per cent)*, add 3 ml of *ethanol*……..

Candesartan Cilexetil Tablets. Page 4426

Assay. *Test solution*

Change **to:** *Test solution***.** Weigh and powder 20 tablets. Disperse a quantity of powder containing 20 mg of Candesartan Cilexitil in about 20 ml of solvent mixture with the aid of ultrasound for 25 minutes with intermittent shaking. Allow to cool and dilute to 25.0 ml with the solvent mixture and filter.

Reference solution
Change **to:** *Reference solution***.** A 0.08 per cent w/v solution of *candesartan cilexetil RS* in the solvent mixture.

Carboplatin. Page 1486

Acidity and Impurity B. Line 3
Change **from:** To solution A add 0.1 ml
to: To 10 ml of solution A, add 0.1 ml

Cetirizine Hydrochloride. Page 1559

Related substances. After chromatographic system, para 1, line 3
Change **from**: the tailing factors are not more than 2.0.
to: the tailing factor is not more than 2.0 for cetirizine peak.

Last para, lines 9 to 11
Change **from:** Ignore any peak with an area 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent).
to: Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Cetirizine Tablets. Page 1561

Related substances. After chromatographic system, para 1, lines 3 and 4
Change **from**: the tailing factors not more than 2.0.
to: the tailing factor is not more than 2.0 for cetirizine peak.

Chloroquine Phosphate Tablets. Page 1589

Dissolution. Line 10
Change **from**: per tablet
to: in the medium

Chloroquine Sulphate Tablets. Page 1592

Dissolution. Line 10
Change **from**: per tablet
to: in the medium

Chlorothiazide. Page 1593

Heavy metals. Line 2
Change **from**: method D
to: method B

Cholecalciferol Injection. Page 1606

Labelling. Last para
Delete the following requirement
"When calciferol injection is prescribed or demanded, Cholecalciferol Injection or Ergocalciferol Injection shall be dispensed or supplied."

Cholecalciferol Tablets. Page 1606

Labelling. Last para
Delete the following requirement
"When calciferol tablets are prescribed or demanded, Cholecalciferol Tablets or Ergocalciferol Tablets shall be dispensed or supplied."

Ciclesonide Inhalation. Page 1614

Line 1
Change **from:** Ciclesonide Inhalation is a suspension of microfine Ciclesonide in a suitable liquid filled in a suitable pressurized container. It may contain suitable pharmaceutical aids such as surfactants, stabilizing agents.
to: Ciclesonide Inhalation is a suspension or solution of microfine Ciclesonide in a suitable liquid filled in a suitable pressurized container. It may contain suitable pharmaceutical aids such as surfactants, stabilizing agents.

Cinacalcet Hydrochloride. Page 1623

Related substances. Impurity table, line 4
Change **from:** 12 minutes
to: 7 minutes

Clarithromycin. Page 1643

Water. Line 2
Change **from:** *pyridine*
to: *methanol*

Clindamycin Capsules. Page 1651

Insert synonym
Clindamycin Hydrochloride Capsules

Para 1
Change **to:** Clindmycin Capsules contain clindamycin hydrochloride equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of clindamycin, $C_{18}H_{33}ClN_2O_5S$.

Clindamycin Phosphate. Page 1654

Appearance of solution. Lines 1 and 2
Change **to:** Solution A is clear (2.4.1) and colourless (2.4.1).

Clotrimazole Lotion. Page 4435

Insert before **Assay**
Other tests. Comply with the tests stated under Lotions.

Colistimethate Sodium. Page 1693

Total sulphite
Delete the requirement.

Pyrogens
Change **from**: *Colistimethate sodium intended for use in the manufacture of parenteral preparation without a further appropriate procedure for the removal of pyrogens complies with the following additional requirement.*

Pyrogens (2.2.8). Complies with the test for pyrogens, using per kg of the rabbit's weight, 1.0 ml of a solution in water for injections containing 2.5 mg of the substance under examination per milliliter.

to: *Colistimethate sodium intended for use in the manufacture of parenteral preparation 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 2.0 Endotoxin Units per mg of colistin.

Cyclophosphamide Injection. Page 1723

pH. Line 1
Change **from:** 4.0 to 6.0
to: 3.0 to 6.0

Diazepam Injection. Page 1802

Identification. A, last para, line 4
Change **from**: 254 nm
to: 365 nm

Dimethicone. Page 1846

Refractive Index
Insert at the end
, determined at 25°.

Docetaxel Injection. Page 1874

Insert before **Other tests**

Bacterial endotoxins (2.2.3). Not more than 1.94 Endotoxin Units per mg of docetaxel (anhydrous).

Enoxaparin Injection. Page 1946

Free sulphate

Change **from**: *Sulphate stock solution*. A 0.1 per cent w/v solution of *sodium sulphate* in the mobile phase. Dilute 5 ml of the solution to 25 ml with the mobile phase.

to: *Sulphate stock solution*. Dissolve an accurately weighed quantity of *sodium sulphate* equivalent to 0.1 g of *sulphate* in 100.0 ml of the mobile phase. Dilute 5.0 ml of the solution to 25.0 ml with the mobile phase.

Erythromycin Stearate. Page 1973

Change **from**: Erythromycin Stearate has a potency not less than 600 Units per mg, calculated on anhydrous basis.

to: Erythromycin Stearate has a potency not less than 600 Units of erythromycin per mg, calculated on anhydrous basis

Ethionamide. Page 1999

Related substances. Last para

Change **to:** Inject the reference solution and the test solution. 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 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).

Ethionamide Tablets. Page 1999

Related substances. Last para

Change **to:** Inject the reference solution and the test solution. 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 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).

Dried Ferrous Sulphate. Page 2050

Definition

Change **from**: Dried Ferrous Sulphate is Ferrous Sulphate from which a part of the water of crystallization has been removed by drying at a temperature of 40°.

to: Dried Ferrous Sulphate is Ferrous Sulphate from which a part of the water of crystallization has been removed by drying.

Finasteride. Page 2057

Related substances

After chromatographic system, Table

Delete- (Retention time: about 28 minutes)

Fluphenazine Decanoate Injection. Page 2098

Related substances. *Reference solution (b),* line 3

Change **from:** fluphenazine impurity A

to: fluphenazine impurity

After chromatographic system, para 1

Change **from:** Inject reference solution (c). The test is not valid unless the resolution between the peaks due to two fluphenazine mono-N-oxides is not less than 2.0.

to: Inject reference solution (c). The test is not valid unless the resolution between the peaks due to mono- N- oxide and di-N-oxide is not less than 2.0.

Para 2, line 3

Change **from:** fluphenazine impurity A

to: fluphenazine impurity

Line 9

Change **from:** The sum of areas of all the secondary peaks is……

to: The sum of areas of all the secondary peaks excluding the peak of fluphenazine impurity is.....

Fluticasone Propionate Inhalation. Page 2112

Usual strengths

Change **from**: 44 µg per metered dose; 110 µg per metered dose; 220 µg per metered dose.

to: 50 µg per metered dose; 125 µg per metered dose; 250 µg per metered dose.

Fluvastatin Capsules. Page 2116

Para 1

Change **from:** Fluvastatin Capsules contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of fluvastatin, $C_{24}H_{26}FNO_4$.

to: Fluvastatin Capsules contain fluvastatin sodium equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of fluvastatin, $C_{24}H_{26}FNO_4$.

Assay. Last line

Change **to:** Calculate the content of $C_{24}H_{26}FNO_4$. Each mg of $C_{24}H_{25}FNNaO_4$ is equivalent to 0.95 mg of $C_{24}H_{26}FNO_4$.

Insert after **Storage**

Labelling. The label states the strength in terms of the equivalent amount of fluvastatin.

Folic Acid and Methylcobalamin Tablets. Page 2122

Insert before **Identification**

NOTE – Carry out the tests in the dark using low actinic glassware.

Storage

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

Gabapentin Capsules. Page 2146

Related substances. Last para, line 4

Change **from:** twice the area of principal peak with the reference solution

to: twice the area of peak due to gabapentin impurity A in the chromatogram obtained with the reference solution

Gabapentin Tablets. Page 2147

Related substances. Last para, line 4

Change **from:** twice the area of principal peak with the reference solution

to: twice the area of peak due to gabapentin impurity A in the chromatogram obtained with the reference solution

Glibenclamide and Metformin Tablets. Page 2172

Dissolution.

For Metformin Hydrochloride. Lines 2 to 4

Change **to:** Medium. 1000 ml, prepared by dissolving 6.8 g of *monobasic potassium phosphate* in 1000 ml of *water* and adjusted to pH 6.8 with *0.2 M sodium hydroxide*,

Granisetron Hydrochloride. Page 4451

pH

Change **from**: determined in solution A.

to: determined in a 1.0 per cent w/v solution.

Granisentron Injection. Page 4453

Line 2

Change **from**: Granisetron

to: Granisetron Hydrochloride

Insulin Zinc Suspension. Page 2294
Insert before **Other tests**
Bacterial endotoxins (2.2.3). Not more than 80 Endotoxin Units per 100 Units of insulin.

Insulin Zinc Suspension (Amorphous). Page 2296
Insert before **Other tests**
Bacterial endotoxins (2.2.3). Not more than 80 Endotoxin Units per 100 Units of insulin.

Insulin zinc Suspension (Crystalline). Page 2297
Insert before **Other tests**
Bacterial endotoxins (2.2.3). Not more than 80 Endotoxin Units per 100 Units of insulin.

Isopropyl Rubbing Alcohol. Page 2328
Specific gravity
Change **from:** 25°
to: 20°

Labetalol Hydrochloride. Page 2365
Heavy metals
Change **to: Heavy metals** (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Letrozole Tablets. Page 2405
Related substances
Insert after impurity table
(NOTE- Letrozole related compound A and 4,4',4"-Methanetriyltribenzonitrile are process impurities and are controlled in the drug substance monograph)

Levocarnitine. Page 4457
Specific optical rotation
Change **from**: +29.0º to +32.0º,
to: –29.0º to –32.0º,

Sodium. After Instrumental conditions, para 1, line 3
Change **from**: potassium
to: sodium

Methadone Injection. Page 2550
Bacterial endotoxins
Change **from**: Not more than 8.8 Endotoxin Units per mg of methadone.
to: Not more than 8.8 Endotoxin Units per mg of methadone hydrochloride.

Metoprolol Succinate. Page 2583
Related substances
Insert at the end
Ignore any peak due to succinic acid.

Misoprostol Tablets. Page 2620
Assay. *Test solution,* line 2
Change **from**: 4 mg
to: 0.4 mg

Line 4
Change **from**: 100.0 ml
to: 10.0 ml

Modafinil Tablets. Page 4470

Assay. After chromatographic system, para 1

Change **from**: The relative retention time of salicylic acid with respect to modafinil is about 1.0.

to: The relative retention time with respect to modafinil for salicylic acid is about 1.1.

Multiple Electrolytes and Dextrose Injection Type I. Page 2641

Assay. *For phosphate***,** line 9

Change **from:** .....of *anhydrous sodium sulphite*, mix....

to: .....of *anhydrous sodium sulphite*, add 5.0 ml of *water*, mix....

Multiple Electrolytes and Dextrose Injection Type III. Page 2644

Assay. *For phosphate***,** line 9

Change **from:** .....of *anhydrous sodium sulphite*, mix....

to: .....of *anhydrous sodium sulphite*, add 5.0 ml of *water*, mix....

Nimodipine. Page 4473

Change **from**: **Specific optical rotation**

to: **Optical rotation**

Ondansetron Orally Disintegrating Tablets. Page 2789

Related substances. After chromatographic system, para 3

Change **to:** Inject reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the area of the peak due to 2-methylimidazole, multiplied with correction factor 1.89, is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.15 per cent), the area of the peak due to ondansetron impurity D, multiplied with correction factor 0.77, is not more than 0.24 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.12 per cent), the area of any other secondary peak is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.2 per cent) and sum of areas of all the secondary peaks is not more than the area of principal peak in the chromatogram obtained with reference solution (d) (0.5 per cent).

D-Panthenol. Page 2847

Refractive index

Change **from:** 1.490 to 1.498, determined at 20^{o}.

to: 1.495 to 1.502, determined at 20^{o}.

Pentoxifylline. Page 4480

Sulphates. Line 1

Change **from**: 1.33 g

to: 0.75 g

Perindopril Erbumine Tablets. Page 4484

Dissolution. Chromatographic system, mobile phase, line 2

Change **from**: 64 volumes

to: 66 volumes

Related substances

Insert before *Test solution*

NOTE- Prepare the solutions immediately before use or maintain at a temperature below 10°.

Phenobarbitone Injection. Page 2902

Bacterial endotoxins

Change **from**: Not more than 0.3 Endotoxin Unit per mg of phenobarbitone.

to: Not more than 0.3 Endotoxin Unit per mg of phenobarbitone sodium.

Phentolamine Injection. Page 2908

Bacterial endotoxins

Change **from**: Not more than 5.8 Endotoxin Units per mg of phentolamine.

to: Not more than 5.8 Endotoxin Units per mg of phentolamine mesylate.

Pirfenidone. Page 2947

Related substances

Insert after chromatographic system

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates and the tailing factor is not more than 2.0 for pirfenidone peak.

Procainamide Injection. Page 2999

Insert before **Other tests**

Bacterial endotoxins (2.2.3). Not more than 0.35 Endotoxin Unit per mg of procainamide hydrochloride.

Promethazine Injection. Page 3015

Bacterial endotoxins

Change **from**: Not more than 5.0 Endotoxin Units per mg of promethazine.

to: Not more than 5.0 Endotoxin Units per mg of promethazine hydrochloride.

Propranolol Injection. Page 3024

Bacterial endotoxins

Change **from**: Not more than 55.6 Endotoxin Units per mg of propranolol.

to: Not more than 55.6 Endotoxin Units per mg of propranolol hydrochloride.

Pyrazinamide. Page 3042

Water

Change **from:** Not more than 0.5 per cent, determined on 5.0 g.

to: Not more than 0.5 per cent, determined on 2.0 g.

Rabeprazole Injection. Page 3079

Water

Change **from:** Not more than 6.0 per cent, determined on 0.1 g.

to: Not more than 7.0 per cent determined on 0.1 g.

Raloxifene Hydrochloride Tablets. Page 3087

Identification. B, line 3

Change **from:** the reference solution.

to: reference solution (b).

Ranitidine Tablets. Page 3098

Dissolution. Last para, line 7

Change **from**: *Ranitidine RS*

to: *Ranitidine hydrochloride RS*

Ritodrine Hydrochloride. Page 3129

Related substances. Impurity table

Change **from:**

Name	Relative retention time
Tyramine	0.3
Hexahydroketone II	0.65
Hexahydroketon I	0.85
Ritodrine hydrochloride	1.0
threo-diastereoisomer	1.15
Aminoketone	2.3

to:

Name	Relative retention time
Ritodrine impurity A[1]	0.3
Ritodrine impurity C[3]	0.7
Ritodrine impurity B[2]	0.9
Ritodrine hydrochloride	1.0
Ritodrine impurity D[4]	1.2
Ritodrine impurity E[5]	2.3

[1]Tyramine
[2]rac-4-[(1R,2R)-2-{[1-hydroxy-1-(4-hydroxyphenyl)propan-2-yl]amino}ethyl]cyclohexan-1-one (hexehydroxketoneI)
[3]rac-4-[(1R,2R)-1-hydroxy-2-{[2-(4-hydroxyphenyl)ethyl]amino}propyl]cyclohexan-1-one (hexehydroketone II)
[4]rac-4-[(1R,2R)-1-hydroxy-2-{[2-(4-hydroxyphenyl)ethyl]amino}propyl]phenol(threo-diastereoisomer)
[5]rac-1-(4-hydroxy)-3-{[2-(4-hydroxyphenyl)ethyl]amino}peopan-1-one (aminoketone).

Last para
Change **to**: Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak due to impurity C, multiplied by correction factor 2.9, is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent). The area of any peak due to impurity A and impurity E, each of is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak due to impurity B, multiplied by correction factor 2.0 and impurity D, each of is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent). The area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Ritodrine Injection. Page 3130

Bacterial endotoxins
Change **from**: Not more than 0.5 Endotoxin Unit per mg of ritodrine.
to: Not more than 0.5 Endotoxin Unit per mg of ritodrine hydrochloride.

Colloidal Silicon Dioxide. Page 4506

Description. Line 2
Change **from:** 15 µm
to: 15 nm

Sodium Chloride. Page 3208

Potassium
Change **to**: **Potassium.** Not more than 0.1 per cent, determined by flame photometry (2.4.4) or by method A for atomic absorption spectrophotometry (2.4.2), using a 1.0 per cent w/v solution and measuring at 767 nm. Use suitable dilutions in water of *potassium solution FP* or *potassium solution AAS* respectively, for the standard solution.

Sodium Citrate Irrigation Solution. Page 3216

Para 1, line 2
Change **from:** water for irrigation
to: water for injections

Monobasic Sodium Phosphate. Page 3232

Arsenic
Change **from**: Dissolve a portion equivalent to 1.25 g of NaH_2PO_4,H_20 in 35 ml of *water.* The solution complies with limit test A for arsenic (8 ppm).
to: Dissolve a portion equivalent to 1.25 g of NaH_2PO_4,H_20 in 35 ml of *water* and add 10 ml of *stannated hydrochloric acid AsT.* The resulting solution complies with limit test for arsenic (8 ppm).

Sodium Valproate Gastro-resistant Tablets. Page 4509

Dissolution
Change **to**: **Dissolution** (2.5.2).

A. Apparatus No. 2,
Medium. 900 ml of *0.1 M hydrochloric acid,*
Speed and time. 100 rpm and 120 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Dilute the filtrate, if necessary, with the dissolution medium to obtain a solution containing 0.001 per cent w/v of Sodium Valproate.

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

Chromatographic system
- a stainless steel column 30 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 45 volumes of buffer solution prepared by dissolving 0.32 g of *potassium dihydrogen orthophosphate* in 100 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid* and 55 volumes of *acetronitrile,*
- flow rate: 2 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 50 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_8H_{15}NaO_2$ in the medium.

Not more than 10 per cent of the stated amount of $C_8H_{15}NaO_2$.

B. Apparatus No. 2,
Medium. Replace *0.1 M hydrochloric acid* with 900 ml of *phosphate buffer pH 6.8,*
Speed and time. 100 rpm and 60 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14), using the chromatographic system as described in Method A.

Test solution. Dilute the filtrate, if necessary, with the dissolution medium to obtain a solution containing 0.002 per cent w/v of Sodium Valproate.

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

Inject the reference solution and the test solution.

Calculate the content of $C_8H_{15}NaO_2$ in the medium.

D. Not less than 70 per cent of the stated amount of $C_8H_{15}NaO_2$.

Solifenacin Succinate Tablets. Page 4511

Related substances. Impurity Table, last line, column 3
Change **from**: 0.8
to: 0.9

Uniformity of content
Test solution. Line 1
Change **from**: Disperse one tablet in 5 ml of *water*,
to: Disperse one tablet in suitable volume of the solvent mixture,

Sorafenib Tosylate. Page 3242

Related substances. After impurity table, lines 2 to 4

Change **from:** [2]4-[4-[[[[2-Chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-phenoxy]-N-6-methyl-2 pyridinecarboxamide tosylate,
[3]1, 3-bis (4-Chloro-3-difluorophenyl)phenyl urea.
to: [2]4-[4-[[2-Chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-N-methyl-pyridine-2-caboxamide, 4-methylbenzene sulfonic acid,
[3]1, 3-bis (4-Chloro-3-(trifluomethyl)phenyl] urea.

Page 4512
Related substances. Chromatographic system, line 2
Change **from**: octadecylsilane
to: octylsilane

Sorafenib Tablets. Page 4512
Related substances. Chromatographic system, line 2
Change **from**: octadecylsilane
to: octylsilane

Assay. Chromatographic system, line 2
Change **from**: octadecylsilane
to: octylsilane

Stearic Acid. Page 3259
Identification. Lines 3 and 4
Change **from:** reference solution (c).
to: the reference solution.

Talc. Page 3303
Acid-soluble substances. Lines 4 to 5
Change **from:** ignite to constant weight.
to: ignite at 800 ± 25° to constant weight.

Water-soluble substances
Change **from:** Shake 5.0 g with 25 ml of *water* for 1 minute, filter, evaporate the filtrate and dry to constant weight; the residue weighs not more than 10 mg.
to: To 10 g add 50 ml of *carbon dioxide-free water*, heat to boiling and maintain boiling under a reflux condenser for 30 minutes. Allow to cool, filter through a medium-speed filter paper and dilute to 50 ml with *carbon dioxide-free water*. Take 25 ml of the filtrate, evaporate to dryness and heat at 105° for 1 hour. The residue weighs a maximum of 10 mg.

Telmisartan and Amlodipine Tablets. Page 4520
Dissolution
For Amlodipine
Chromatographic system, mobile phase, line 2
Change **from**: 0.022 g
to: 3.43 g

For Telmisartan
Medium, line 2
Change **from**: *0.05 M*
to: 6.8 g

Line 3
Change **from**: *0.038 M*
to: 1.52 g

Teneligliptin Tablets. Page 4523
Related substances. Last para
Insert at the end
Ignore any peak due to hydrobromic acid obtained with the test solution at relative retention time about 0.09.

Thiamine Injection. Page 3355

Assay. After chromatographic system, line 1
Change **from:** $C_{12}H_{17}ClN_4OS$.
to: $C_{12}H_{17}ClN_4OS$, HCl

Thiamine Tablets. Page 3355

Assay. After chromatographic system, line 1
Change **from:** $C_{12}H_{17}ClN_4OS$.
to: $C_{12}H_{17}ClN_4OS$, HCl

Timolol Eye Drops. Page 3378

Identification. A, para 2, lines 3 and 4
Change **from**: *timolol RS* or with the reference spectrum of timolol.
to: *timolol maleate RS,* treated in the same manner or with the reference spectrum of timolol.

Timolol Tablets. Page 3379

Identification. A, para 2, lines 3 and 4
Change **from**: *timolol RS* or with the reference spectrum of timolol.
to: *timolol maleate RS,* treated in the same manner or with the reference spectrum of timolol.

Tizanidine Tablets. Page 3385

Uniformity of content
Reference solution
Change **to:** *Reference solution.* Dissolve about 10 mg of *tizanidine hydrochloride RS*, in 25 ml of *phosphate buffer pH 6.6* and dilute to 50.0 ml with *acetonitrile*. Dilute a suitable volume of the solution in a mixture of equal volumes of *phosphate buffer pH 6.6* and *acetonitrile* to obtain a concentration similar to the test solution.

Tranexamic Acid. Page 3415

Chlorides
Change **from:** Dissolve 1.8 g in 50 ml of *water*, the solution complies with the limit test for chlorides (140 ppm).
to: 1.8 g complies with the limit test for chlorides (140 ppm).

Tranexamic Acid Injection. Page 3416

Related substances. Impurity table
Change **to**:

Name	Relative retention time	Correction factor
Tranexamic acid (Retention time: about 13 minutes)	1.0	--
Tranexamic acid impurity C[1]	1.1	--
Tranexamic acid impurity D[2]	1.3	--
Tranexamic acid impurity B[3]	1.5	1.2
Tranexamic acid impurity A[4]	2.1	--

Tranexamic Acid Tablets. Page 3417

Related substances. Impurity table
Change **to**:

Name	Relative retention time	Correction factor
Tranexamic acid (Retention time: about 13 minutes)	1.0	--
Tranexamic acid impurity C[1]	1.1	--
Tranexamic acid impurity D[2]	1.3	--
Tranexamic acid impurity B[3]	1.5	1.2
Tranexamic acid impurity A[4]	2.1	--

Vancomycin Intravenous Infusion. Page 3479

Insert the following after para 1

Vancomycin Intravenous Infusion contains not less than 90.0 per cent and not more than 115.0 per cent of the stated amount of vancomycin, $C_{66}H_{75}C_{12}N_90_{24}$.

Venlafaxine Prolonged-release Capsules. Page 4526

Identification. Para 2, line 8

Change **from**: heated

to: treated

Releted substances

Reference solution (b), line 2

Change **from**: (containing impurity D)

to: (containing impurity D and F)

Venlafaxine Prolonged-release Tablets. Page 4527

Identification. Para 2, line 8

Change **from**: heated

to: treated

Releted substances

Reference solution (b), line 2

Change **from**: (containing impurity D)

to: (containing impurity D and F)

Venlafaxine Tablets. Page 4528

Identification. Para 2, line 8

Change **from**: heated

to: treated

Releted substances

Reference solution (b), line 2

Change **from**: (containing impurity D)

to: (containing impurity D and F)

Vinorelbine Injection. Page 3496

Bacterial endotoxins

Change **from**: Not more than 3.0 Endotoxin Units per mg of vinorelbine tartrate.

to: Not more than 3.0 Endotoxin Units per mg of vinorelbine.

Voriconazole Injection. Page 3507

After **Description**, para 1, line 3

Change **from:** (Injections)

to: (Powder for Injections)

Other tests. **Delete** the requirement

Zinc Oxide Cream. Page 3541

Line 2

Change **from**: w/v

to: w/w

Zopiclone Tablets. Page 3559

Insert before **Related substances**

D. Not less than 70 per cent of the stated amount of $C_{17}H_{17}ClN_6O_3$.

Sterile Water for Injections. Page 3518

Tests

Ammonium
Change **to**: **Ammonium**. For containers with a nominal volume less than 50 ml: maximum 0.6 ppm; for containers with a nominal volume equal to or greater than 50 ml: maximum 0.2 g per litre.

Containers with a nominal volume less than 50 ml: To 20 ml, add 1 ml of *alkaline potassium tetraiodomercurate solution* and allow to stand for 5 minutes. When viewed vertically the solution is not more intensely coloured than a solution prepared at the same time by adding 1 ml of *alkaline potassium tetraiodomercurate solution* to a mixture of 4.0 ml of *ammonium standard solution* (*3 ppm NH_4*) and 16.0 ml of *ammonia-free water* (0.6 ppm).

Containers with a nominal volume equal to or greater than 50 ml: To 20 ml, add 1 ml of *alkaline potassium tetraiodomercurate solution* and allow to stand for 5 minutes. When viewed vertically the solution is not more intensely coloured than a solution prepared at the same time by adding 1 ml of *alkaline potassium tetraiodomercurate solution* to a mixture of 4.0 ml of *ammonium standard solution* (*1 ppm NH_4*) and 16.0 ml of *ammonia-free water* (0.2 ppm).

Chlorides
Para 2, **Insert** at the end
For containers with a nominal volume greater than 100 ml, use the following test: to 10 ml add 1 ml of *dilute nitric acid* and 0.2 ml of *silver nitrate solution*. The solution shows no change in appearance for at least 15 minutes.

Aluminium
Insert after **Sulphates**
Aluminium. Maximum 10 ppb, if intended for use in the manufacture of dialysis solutions.
Prescribed solution to 400 ml of the water to be examined add 10 ml of acetate buffer solution pH 6.0 and 100 ml of *distilled water*.

Reference solution. Mix 2 ml of *aluminium standard solution* (*2 ppm Al*), 10 ml of *acetate buffer solution pH 6.0* and 98 ml of *distilled water*.

Blank solution. Mix 10 ml of *acetate buffer solution pH 6.0* and 100 ml of *distilled water*.

Adsorbed Pertussis Vaccine (Acellular Component). Page 3587

Production, General provisions
Para 1, **Insert** at the end
Where a genetically modified form of B. Pertussis is used, production consistency and genetic stability shall be in conformity with the requirements prescribed by the National Regulatory Authority.

CHARACTERISATION OF COMPONENTS
Pertussis toxin, para1
Change **to:** It may be demonstrated by Chinese hamster ovary (CHO) cell-clustering effect and haemagglutination as *in vitro* methods; lymphocytosis-promoting activity, histamine-sensitising activity and insulin secretory activity as *in vivo* methods. The toxin shows ADP- ribosyl transferase activity using transducin as the acceptor.

Filamentous Haemagglutinin, line 2
Change **to**: Pertactin, fimbrial-2 and fimbrial-3 antigens may be demonstrated by reactivity with specific antibody.

FINAL LOT
Identification, line 3
Change **from**: *sodium citrate* to give a 10 per cent w/v solution;
to: *sodium citrate* to give a 1 per cent w/v solution;

Assay. Para 1, **Insert** at end
or any other validated serological assay in guinea pigs or mice as approved by National Regulatory Authority may also be used.

Where a single dilution assay is used production and test consistency over time shall be monitored via suitable indicators and carrying out a full multidilution assay periodically for example every two years.

ELISA
Para 1, line 7
Change **from**: are made on the plates.
to: are made on the plates. Reference antiserum shall be included in each plate.

Inactivated Hepatitis B Vaccine. Page 3630

PROPAGATION AND HARVEST
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Inactivated Influenza Vaccine (Split Virion). Page 3632

PROPAGATION AND HARVEST
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Inactivated Influenza Vaccine (Surface Antigen). Page 3634

PROPAGATION AND HARVEST
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Inactivated Influenza Vaccine (Whole Virion). Page 3636

PROPAGATION AND HARVEST
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Influenza Vaccine (Human, Live Attenuated). Page 3638

PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Japanese Encephalitis Vaccine (Human). Page 3640

SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Japanese Encephalitis Live Vaccine (Human). Page 3642

PROPAGATION AND HARVEST
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Japanese Encephalitis Vaccine Inactivated (Adsorbed, Human). Page 3645

SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Measles Vaccine (Live). Page 3649

SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Mumps Vaccine (Live). Page 3661
SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Poliomyelitis Vaccine, Live (Oral). Page 3676
PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Rabies Vaccine, Human. Page 3682
SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

Rotavirus Vaccine (Live attenuated, Oral). Page 3686
VIRUS SEED LOTS. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

VIRUS PROPAGATION AND HARVEST
Insert before **Virus concentration**
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Rubella Vaccine (Live). Page 3689
SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Tick-borne Encephalitis Vaccine (Inactivated). Page 3699
SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Yellow Fever Vaccine. Page 3714
SEED LOT. Identification
Insert at the end
Mycoplasma (2.7.4). Complies with the test for absence of mycoplasma.

PROPAGATION AND HARVEST. Identification
Insert at the end
Mycoplasma (2.7.4).Complies with the test for absence of mycoplasma.

Castor Oil. Page 3767
Light absorption. Line 3
Change **from**: not more than 0.7 and 1.5.
to: between 0.7 to1.5.

Ginkgo Dry Extract. Page 4544

Assay. formula

Delete "10"

Henna Dry powder. Page 4546

Assay. *Test solution,* line 2

Change **from**: *ethyl acetate*

to*: methanol*

Filgrastim Concentrated Solution. Page 3977

Identification. E

Test solution. Line 5

Change **from** : ....dilute to 1ml with *water....*

to: ....dilute to100 µl with *water.....*

Follicle Stimulating Hormone Concentrated Solution. Page 3991

Para 2, lines 4 and 5

Change **from**: .....contains not less than 0.4 mg and not more than 0.8 mg of protein content per ml of the solution ..... per of protein

to: .....contains not less than 0.1 mg and not more than 0.8 mg of protein content per ml of the solution ..... per of protein

Pegfilgrastim. Page 4038

Identification. B

Change **from**: Determine by isoelectric focusing (2.4.33) capillary electrophoresis.

to: Determine by isoelectric focusing (2.4.33).

E. Line 1

Change **from**: Equilibrate a PD-10 column....

to: Equilibrate any desalting column....

Tests

Impurities with charges differing from that of pegfilgrastim.

Determine by isoelectric focusing (2.4.33).

Reference solution (a).

Change **from**: A solution of *filgrastim RS* containing 0.3 mg per ml.

to: A solution of *pegfilgrastim RS* containing 0.3 mg per ml.

Reference solution (b).

Change **from:** A solution of *filgrastim RS* containing 0.3 mg per ml.

To: A solution of *pegfilgrastim RS* containing 0.3 mg per ml.

Detection. Para 2, line 4

Change **from:** ..... the pI of the principal band is 7.4 – 7.8.

to: .....the pI of the principal band is 5.7- 6.3.

Sodium Chromate (^{51}Cr) Injection. Page 4559

Assay for sodium chromate

Reference solution (b). Lines 1 to 3

Change **from**: Pipet 0.25, 0.50, 0.75, 0.1, 0.125 and 0.150 ml of the reference solution (a) accurately measured into separate 100-ml volumetric flasks.

to: Pipette 0.025, 0.05, 0.075, 0.10, 0.125 and 0.150 ml of the reference solution (a), accurately measured into separate 100-ml volumetric flasks.

Amprolium Oral Powder. Page 4196

Identification. Line 3

Change **from:** the reference solution

to: reference solution (b)

Assay. After chromatographic system, para 1
Change **from:** Inject reference solutions (a) and (b). The test is not valid unless the column efficiency is not less than 6500 theortical plates, the tailing factor is not more than 2.3 and the relative standard deviation is not more than 1.0 per cent. The resolution between amprolium and 2-picoline is not less than 7.0.

Inject reference solution (a) and the test solution.

to: Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to amprolium and 2-picoline is not less than 7.0 in the chromatogram obtained with reference solution (a), the column efficiency is not less than 6500 theoretical plates, the tailing factor is not more than 2.3 and the relative standard deviation is not more than 1.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution.

Cloprostenol Injection. Page 4215

Insert before **Other tests**
Bacterial endotoxins (2.2.3). Not more than 2500 Endotoxin Units per mg of cloprostenol.

Furazolidone Premix. Page 4242

Usual strengths
Change **from:** 4.4 per cent w/v; 22.4 per cent w/v
to: 4.4 per cent; 22.4 per cent

Assay. Para 2
Delete the requirement.

Moxidectin. Page 4262

Related substances
Method A. *Reference solution (b),* lines 1 and 2
Change **from:** *moxidectin RS* (containing impurities A, B, C, D, E, F, G, H, I, J and K)
to: *moxidectin for system suitability RS* (containing impurities A, B, C, D, E, F, G, H, I, J and K)

Method B. *Reference solution (b),* lines 1 and 2
Change **from:** *moxidectin RS* (containing impurities A, B, C, D, E, F, G, H, I, J and K)
to: *moxidectin for system suitability RS* (containing impurities A, B, C, D, E, F, G, H, I, J and K)

Heavy metals
Change **to: Heavy metals** (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash
Change **from:** Not more than 2.0 per cent.
to: Not more than 0.2 per cent.

Tylosin Injection. Page 4299

Insert before **Other tests**
Bacterial endotoxins (2.2.3). Not more than 0.28 Endotoxin Unit per mg of tylosin.