INDIAN PHARMACOPOEIA COMMISSION
MINISTRY OF HEALTH & FAMILY WELFARE, GOVERNMENT OF INDIA
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Date: 02.01.2019

To,

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

Subject: Amendment List-003 to IP 2018

As you are aware that 8th Edition of Indian Pharmacopoeia (IP) 2018 has become effective from 1st January 2018. Based on scientific inputs, some monographs needed up-gradation and accordingly Amendment List-003 is issued containing such amendments.

This is for notice and compliance with IP 2018.

(Dr. G. N. Singh)
Secretary-cum-Scientific Director

Encl. Amendment List-003 to IP 2018

Amendment List 003 to IP-2018

2.3.18. Sulphated Ash. Page 140

Change **to**: Ignite a suitable crucible (for example, silica, platinum, porcelain or quartz) at 600 ± 50° for 30 minutes, allow to cool in a desiccator over silica gel or other suitable desiccant and weigh. Place the prescribed amount of the substance to be examined in the crucible and weigh. Moisten the substance under examination with a small amount of *sulphuric acid* (usually 1 ml) and heat gently at as low a temperature as practicable until the sample is thoroughly charred. After cooling, moisten the residue with a small amount of *sulphuric acid* (usually 1 ml), heat gently until white fumes are no longer evolved and ignite at 600 ± 50° until the residue is completely incinerated. Ensure that flames are not produced at any time during the procedure. Allow the crucible to cool in a desiccator over silica gel or other suitable desiccant, weigh it again and calculate the percentage of residue.

If the amount of the residue so obtained exceeds the prescribed limit, repeat the moistening with sulphuric acid and ignition, as previously, for 30 minutes periods until 2 consecutive weighing do not differ by more than 0.5 mg or until the percentage of residue complies with the prescribed limit.

The amount of substance used for the test (usually 1-2 g) is chosen so that at the prescribed limit the mass of the residue (usually about 1 mg) can be measured with sufficient accuracy.

2.4.17 .Thin-Layer Chromatography. Page 204

Test for Related substances.
Insert the following at the end

Secondary spots - A secondary spot is a spot in the chromatogram other than the principal spot and any spots due to internal standard, solvent or derivatising agents. If justified, spots 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. Page 220

Ondansetron Hydrochloride. Page 241, line 2

Change **from**: sparingly
to: slightly

Tenofovir Disoproxil Fumarate. Page 248

Change **from**: soluble in *water*
to: Freely soluble in *dimethyl formamide* and *methanol*; sparingly soluble in *water*.

Adrenaline Tartrate. Page 1165

Identification. B, line 2

Change **from**: 0.005 per cent
to: 0.003 per cent

Line 4
Change **from**: 0.4
to: 0.45

Adrenaline Injection. Page 1166

Identification. A

Change **to**: In the Assay, the principal peak in the chromatogram obtained with the test solution corresponding to the principal peak in the chromatogram obtained with reference solution (a).

Albendazole Tablets. Page 1170

Lines 1 and 2
Change **from**: Albendazole Tablets contain Albendazole. The tablets may contain permitted flavouring agents.
to: Albendazole Tablets contain Albendazole. The tablets may be chewable and may contain permitted flavouring and sweetening agents.

Under **Tests** Insert

Dissolution (2.5.2).
Apparatus No. 1,
Medium. 900 ml of *0.1 M hydrochloric acid*,
Speed and time.75 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter. Dilute 1.0 ml of filtrate to 50.0 ml with *0.1 M sodium hydroxide*. Measure the absorbance of the resulting solution at the maximum at about 308 nm (2.4.7). Calculate the content of $C_{12}H_{15}N_3O_2S$ per tablet taking 742 as the specific absorbance at 308 nm.

D. Not less than 80 per cent of the stated amount of $C_{12}H_{15}N_3O_2S$.

Labelling.
Change **from**: The label states that the tablets should be chewed before swallowing.
to: The label states, wherever applicable, the tablets should be chewed before swallowing

Alfacalcidol. Page 1170

Assay. Para 2
Change **from**: Inject reference solution (c). The test is not valid unless the relative standard deviation for replicate injections is not more than 1.0 per cent.
to: Inject reference solution (c). The test is not valid unless the resolution between the peaks due to pre-alfacalcidol and alfacalcidol is not less than 4.0.
Para 3
Change **from**: Inject reference (a), (c) and the test solution.
to: 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 reference solution (a) and the test solution.

Dried Aluminium Hydroxide. Page 1185

Add Synonym

Dried Aluminium Hydroxide Gel

Aluminium Hydroxide Gel. Page 1186

Delete Synonym
Dried Aluminium Hydroxide Gel

Amiloride Tablets. Page 1203

Related substances. *Reference solution (a)*

Change **from**: A 0.175 per cent w/v solution of *amiloride hydrochloride RS* in the solvent mixture.

to: A solution of *amiloride hydrochloride RS* containing 0.175 per cent w/v of anhydrous amiloride hydrochloride in the solvent mixture.

Amiodarone Hydrochloride. Page 1210

Appearance of solution. Line 1

Change **from**: A 5.0 per cent w/v solution.

to: A 5.0 per cent w/v solution in *methanol*.

Anticoagulant Citrate Phosphate Dextrose Adenine Solution. Page 1252

Assay. *For sodium dihydrogen phosphate dehydrate*, after line 15

Change **from**: 25 C (A1/A2)

to: 22.92 C(A1/A2)

Aspirin and Caffeine Tablets. Page 1278

Insert the following, before **Salicylic acid**.

Dissolution (2.5.2).
For aspirin—

Apparatus No. 1,
Medium. 500 ml of a pH 4.5 buffer prepared by dissolving 2.99 g of *sodium acetate* and 1.66 ml of *glacial acetic acid* in sufficient *water* and dilute to 1000 ml with *water*,
Speed and time. 50 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtered solution, suitably diluted with the dissolution medium, if necessary, at the maximum at about 265 nm (2.4.7). Calculate the content of $C_9H_8O_4$ in the medium from the absorbance obtained from a solution of known concentration of *aspirin RS* in the dissolution medium in such manner to get similar concentration of the test solution.

D. Not less than 75 per cent of the stated amount of $C_9H_8O_4$.

Atazanavir Capsules. Page 1280

Related substances. *Reference solution.*

Change **from**: A 0.001 per cent w/v solution of *atazanavir sulphate RS* in the solvent mixture.

to: A solution of *atazanavir sulphate RS* containing 0.001 per cent w/v of atazanavir in the solvent mixture.

Betahistine Hydrochloride. Page 1360

Heavy metals. Line 2

Change **from**: Method C

to: Method B

Bisacodyl Suppositories. Page 1390

Related substances. Last para, line 2

Change **from**: examine under UV light at 254 nm.

to: spray with a mixture of equal volumes of *0.05 M iodine* and *dilute sulphuric acid* and examine the plate in day light.

Bisacodyl Gastro-resistant Tablets. Page 1390

Insert the following, before **Related substances**.

Dissolution (2.5.2).

A. Apparatus No. 2,

Medium. 500 ml of *0.1 M hydrochloric acid,*

Speed and time.100 rpm and 120 minutes.

Withdraw a suitable volume of medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Dilute the filtrate, if necessary, with the dissolution medium.

Reference solution. Dissolve about 50 mg of *bisacodyl RS* in 50 ml of *methanol,* add a drop of *orthophosphoric acid* and dilute with *0.1 M hydrochloric acid* to obtain 0.0005 per cent w/v solution of bisacodyl.

Chromatographic system

- a stainless steel column 10 cm x 4.0 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil C18),
- column temperature: 40º,
- mobile phase: a mixture of 35 volumes of 0.1 per cent w/v solution of *ammonium acetate*, adjusted to pH 8.0 with *dilute ammonia solution* and 65 volumes of *acetonitrile,*
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{19}NO_4$ in the medium.

After completion of A, remove the basket from the vessel and dip once into a 100 ml beaker containing 80 ml of *water*. After the water has drained from the basket, transfer the tablets to Apparatus No. 1 and carry out the procedure described under B.

B. Apparatus No.1,

Medium. 900 ml of a buffer solution prepared by dissolving 8.9 g of *disodium hydrogen orthophosphate* and 10 g of *sodium lauryl sulphate* in 800 ml of *water*, adjusted to pH 7.5 with *0.1 M hydrochloric acid* and dilute to 1000 ml with *water*.

Speed and time.100 rpm and 60 minutes.

Withdraw a suitable volume of medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Dilute the filtrate, if necessary, with the dissolution medium.

Reference solution. Dissolve about 50 mg of *bisacodyl RS* in 50 ml of *methanol* add a drop of *orthophosphoric acid* and dilute with dissolution medium to obtain a 0.0056 per cent w/v solution of bisacodyl.

Use chromatographic system as described under A.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{19}NO_4$ in the medium.

D. Not less than 75 per cent of the stated amount of $C_{22}H_{19}NO_4$.

Assay. After Chromatographic system, para1, line 2
Change **from**: less
to: more

Buspirone Tablets. Page1428

Dissolution. Medium.
Change **from**: 0.01 *M hydrochloric acid.*
to: 500 ml of *0.01 M hydrochloric acid.*

Calcium Levulinate. Page 1461

Identification
Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6).
Compare the spectrum with that obtained with *calcium levulinate RS* or with the reference spectrum of Calcium Levulinate
B. It gives reaction (A) of calcium salts (2.3.1).

Calcium Levulinate Injection. Page 1461

Identification B. **Delete** the requirement.
C.
Change **from**: C
to: B

Carbimazole. Page 1482

Identification B. Line 4

Change **from**: reference solution (b).

to: reference solution (c).

Thiamazole and other related substances. *Reference solution (a)*
Change **to**: *Reference solution (a).* Dilute 1.0 ml of 0.005 per cent w/v solution of thiamazole (carbimazole impurity A) in the solvent mixture, and 2.0 ml of test solution to 10.0 ml with the solvent mixture.

After chromatographic system, para 2

Insert at end.

The sum of areas of all the secondary peaks is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent). Ignore any peak with area less than 0.05 times the area of principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent)

Assay.

Change **to**: Determine by liquid chromatography (2.4.14), as described in the test of Related substances with the following modifications.

Reference solution. Dissolve 5 mg of carbimazole RS to 10.0 ml with the solvent mixture.

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 $C_7H_{10}N_2O_2S$.

Carbimazole Tablets. Page 1483

Thiamazole and other related substances. Chromatographic gradient system,

Change **to**:

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
4.6	100	0
30	0	100
30.1	100	0
40	100	0

Uniformity of content.

Change **to**: (*For tablets containing 10 mg or less*).Complies with the test stated under Tablets.

Determine by liquid chromatography (2.4.14), using the chromatographic conditions as described in the test for Thiamazole and other related substances.

Test solution. Disperse one tablet in 10.0 ml of *acetonitrile* with the aid of ultrasound for 5 minutes and filter. Dilute 1.0 ml of this solution to 10.0 ml with mobile phase A.

Inject reference solution (a) and the test solution.

Calculate the content of $C_7H_{10}N_2O_2S$ in the tablet.

Assay.

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

NOTE - Protect the solutions from light and prepare immediately before use.

Test solution. Disperse a quantity of the powdered tablets containing 20 mg of Carbimazole in 10.0 ml of *acetonitrile* with the aid of ultrasound for 5 minutes and filter. Dilute 5.0 ml of this solution to 200.0 ml with mobile phase A.

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

Reference solution (b). A solution containing 0.01 per cent w/v of *carbimazole RS* and 0.0005 per cent w/v of *thiamazole* in mobile phase A.

Use chromatographic conditions as described in the test for Thiamazole and other related substances.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to thiamazole (carbimazole impurity A) and carbimazole is not less than 5.0.

Inject reference solutions (a) and the test solution.

Calculate the content of $C_7H_{10}N_2O_2S$ in the tablets.

Carbomers. Page 1484

Free acrylic acid. Chromatographic system

Change **from**:

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
8	0	100
9	0	100
20	100	0
21	100	0
30	0	100
32	100	0

Change **to**:

Time	Mobile phase A	Mobile phase B

(in min.)	(per cent v/v)	(per cent v/v)
0	100	0
8	100	0
9	0	100
20	0	100
21	100	0
30	100	0

Chlorambucil Tablets. Page 1568

Identification.

Change to: In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Cilnidipine Tablets. Page 1617

Dissolution (2.5.2). Para 1, line 5

Change **from**: *orthophophorus acid*

to: *orthophosphoric acid*

Clindamycin Injection. Page 1655

Assay. *Reference solution (b)*. Line 3

Change **from**: w/v

to: v/v

Clobetasol Cream. Page 1659

Assay. *Test solution (a),* lines 6 and 7

Change **from**: *water* (Solution may assume a gel - like appearance).

to: *ethanol*

Test solution (b), line 4

Delete. (Solution may assume a gel - like appearance)

Reference solution, line 4

Delete. (*50 per cent*)

Clobetasol Ointment. Page 1660

Assay. *Test solution*, line 6

Change **from**: *water*. Solution may assume a gel-like appearance.

to: *ethanol*.

Reference solution (a), line 4

Delete. (*50 per cent*)

Clobetasone Cream. Page 1662

Assay. *Test solution (a)*, lines 6 and 7

Change **from**: *water* (solution may assume a gel-like appearance).

to: *ethanol*

Test solution (b), lines 3 and 4

Delete. (Solution may assume a gel - like appearance)

Reference solution, line 4
Delete. (*50 per cent*)

Colchicine Tablets.Page1691

Insert the following, before **Related substances**

Dissolution (2.5.2).

Apparatus No. 1,

Medium. 500 ml of a pH 6.8 buffer prepared by dissolving 3.52 g of *sodiumdihydrogen orthophosphate monohydrate* and 4.35 g of *disodium hydrogen orthophosphate dihydrate* in sufficient water and dilute to 1000 ml with*water*,

Speed and time.75 rpm and 45 minutes.

Withdraw a suitable volume of medium and filter.

Determine by liquid chromatography (2.4.14).

Note: Protect the following solutions from light.

Test solution. Dilute the filtrate, if necessary, with the dissolution medium.

Reference solution. Weigh a quantity of *colchicine RS* and dilute with the dissolution medium to obtain a solution having a known concentration similar to the test solution.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm), (such as Lichrosorb RP8),
- mobile phase: A. *water,*
  B. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 243 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	52	48
12	52	48
25	20	80
30	20	80
32	52	48
38	52	48

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{25}NO_6$ in the medium.

D. Not less than 75 per cent of the stated amount of $C_{22}H_{25}NO_6$.

Daclatasvir Dihydrochloride. Page 1746

Related substances. Chromatographic system

- injection volume:

Change **from**: 20 ml
to: 20 µl

Assay. Chromatographic system

- injection volume:

Change **from**: 10 ml

to: 10 µl

Disodium Edetate. Page 1858

Impurity A. Change **to**:

Impurity A. Determine by liquid chromatography (2.4.14).

NOTE- Carry out the test protected from light.

Solvent A. A 1.0 per cent w/v solution of *cupric nitrate* in *water.*

Test solution. Dissolve 100 mg of the substance under examination in 10.0 ml of solvent A and sonicate to dissolve.

Reference solution (a). Transfer 100 mg of *nitrilotriacetic acid* to a 10-ml volumetric flask, add 0.5 ml of *ammonium hydroxide*, mix and dilute with *water* to volume.

Reference solution (b). Transfer 1g of disodium edetate to a 100-ml volumetric flask, add 100 µl of reference solution (a), dilute with solvent A and sonicate to dissolve.

Reference solution (c).Transfer 10 mg of disodium edetate to a 100-ml volumetric flask, add 100 µl of reference solution (a), dilute with solvent A and sonicate to dissolve.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (1.5 to 10 µm),
- mobile phase: dilute 10 ml of *1M tetrabutylammonium hydroxide* in *methanol* to 200.0 ml with *water,* adjusted to pH 7.5 ± 0.1with *dilute orthophosphoric acid*, add 90 ml of *methanol* and dilute to 1000 ml with *water*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 50 µl.

The relative retention time with reference to edetate for nitrilotriacetic acid and copper is about 0.35 and 0.65, respectively.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to nitrilotriacetic acid and copper is not less than 3.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution the area of peak corresponding to nitrilotriacetic acid is not more than difference between the area of nitrilotriacetic acid peak obtained from reference solution (b) and the test solution (0.1 per cent).

Docetaxel Trihydrate. Page 1873

Related substances. After chromatographic system

Change **to**:

Name	Relative retention time	Correction factor
Docetaxel impurity A[1]	0.97	1.6
Docetaxel (Retention time is about 27 minutes)	1.0	---
Docetaxel impurity B[2]	1.08	-
Docetaxel impurity C[3]	1.13	-
Docetaxel impurity D[4]	1.18	-

[1]2-*O*-desbenzoy1-2-*O*-tiglyldocetaxel,
[2] 10-deoxy- 10-oxodocetaxel,
[3]7-*epi*-docetaxel
[4]4-*epi*-6-oxodocetaxel

After chromatographic system, para 2, line 8.
Insert the following.

The area of any peak due to docetaxel impurity D is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent).

Drospirenone and Ethinylestradiol Tablets. Page 1908

Related substances. After Chromatographic system

Change **to**:

Name	Relative Retention time	Correction factor	Limit NMT%[a]	Limit NMT%[b]	Detector mode
EthinylEstradiol Degradation					
6 α -hydroxyethinyl estradiol[1]	0.25	1.37	0.3	0.3	FI (215nm/ 315 nm)
6β-hydroxyethinylestradiolis[2]	0.27	1.56	0.3	0.3	FI(215nm/315nm)
6-keto ethinyl estradiol[3]	0.41	0.43	1.5	0.5	UV222 nm
Ethinylestradiol impurity B[4]	0.88	---	1.0	1.0	FI (215 nm/ 344 nm)
Ethinylestradiol	1.0	---	---	---	FI (215nm/ 315 nm) and UV 222 nm
Any unspecified degradation product	---	1.0	0.3	0.5	FI(215nm/315nm) and UV 222 nm
Total degradation product	---	---	3.0	2.5	
Drospirenone Degradation Products					
Drospirenone	0.75	---	---	---	UV 222 nm
17-epidrospirenone[5]	0.83	1.0	0.3	0.3	UV 222 nm
Any unspecified degradation product	---	1.0	0.3	0.5	UV 222 nm
Total degradation Products	---	---	0.5	1.0	

[a]Limits for drug products labeled to contain 3 mg of drospirenone and 0.03 mg of ethinylestradiol.

[b]Limits for drug products labeled to contain 3 mg of drospirenone and 0.02 mg of ethinylestradiol.

[1]19-Nor-6α,17α-pregna-1,3,5(10)-trien-20-yne-3,6,17-triol,

[2] 19-Nor- 6β,17α - pregna-1,3,5(10)-trien-20-yne-3,6,17-triol,

[3]19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol-6-one,

[4]Δ 9,11-Ethinyl estradio1.19-Nor-17α-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol.

[5]17-Hydroxy-6β,7β:15β,16β-dimethylene-3-oxo-17β-pregn-4-ene-21-carboxylic acid, γ-lactone,

Fl = Florescence Detector

UV= Ultraviolet Detector

Ephedrine Hydrochloride. Page 1952

Identification. *Solution A*.

Change **from**: A 0.01 per cent w/v solution in *water*.

to: A 10.0 per cent w/v solution in *water*.

Enrofloxacin Injection. Page 4234

pH (2.4.24).

Change **from**: 9.0 to11.0

to: 9.0 to12.0

Assay. Under Chromatographic condition, mobile phase

Change **from**: a mixture of 85 volumes of *phosphoric acid* and 15 volumes of *acetonitrile*,

to: a mixture of 85 volumes of 0.1 per cent v/v solution of *orthophosphoric acid* and 15 volumes of *acetonitrile*,

Esmolol Hydrochloride. Page 1980

pH (2.4.24).

Change **from**: 1.0 per cent w/v solution.

to: 25.0 per cent w/v solution.

Esomeprazole Gastro-resistant Capsules. Page1983

Change **from**: **Dissolution** (2.5.2). Complies with the test stated under Capsules.

to: **Dissolution** (2.5.2).

A. Apparatus No. 1,

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

Speed and time.100 rpm and 2 hours.

Tap the granules from a capsule slightly with a glass rod to make them settle to the bottom. Rotate the paddle at 100 rpm for 2 hours, drain the solution slowly without losing any granules. Transfer them quantitatively to a 100-ml volumetric flask, add 20 ml of *0.1 M sodium hydroxide* and mix with the aid of ultrasound. Dilute to volume with *0.1 M sodium hydroxide,* centrifuge about 15 ml for 5 minutes and dilute 5.0 ml of the clear supernatant liquid to 50.0 ml with the mobile phase. Using the resulting solution as the test solution, carryout the determination as described in the Assay. Calculate the content of $C_{17}H_{19}N_3O_3S$ in the supernatant liquid. Calculate the percentage of esomeprazole released in the acid medium by subtracting the content of $C_{17}H_{19}N_3O_3S$ in the test solution from the total content of esomeprazole determined in the Assay.

Complies with the acceptance criteria given under acid stage.

B. Apparatus No. 1,
Medium. 900 ml *of phosphate buffer pH 6.8,*
Speed and time.100 rpm and 45 minutes.

Tap the granules from a capsule slightly with a glass rod to make them settle to the bottom. Rotate the paddle at 100 rpm for 45 minutes and filter the solution. Immediately transfer 5.0 ml of the solution to a test tube containing 1.0 ml of *0.*1 *M sodium hydroxide.* Prepare the standard solution having a known concentration similar to the expected concentration and in similar manner to the test solution. Calculate the content of $C_{17}H_{19}N_3O_3S$ in the medium.

D. Not less than 70 per cent of the stated amount of $C_{17}H_{19}N_3O_3S$.

Glibenclamide and Metformin Tablets. Page 2172

Related substances. *For Glibenclamide-*

After chromatographic system, line 1

Change **from**:

Name	Relative retention time	Correction factor
Glibenclamide related compound A[1]	0.30	1.25

to:

Name	Relative retention time	Correction factor
Glibenclamide related compound A[1]	0.30	0.83

Glipizide. Page 2180

Assay. Line 4
Insert at the end
Carry out a blank titration.

Ibuprofen and Paracetamol Tablets. Page 2266

Related substances. Last para
Change **to**: Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to p-amino phenol, p-nitro phenol, p-chloroacetanilide and ibuprofen impurity J, A, B are not more than the area of the principal peak of paracetamol and ibuprofen, respectively in the chromatogram obtained with reference solution (b) (0.3 per cent). The area of any other secondary peak is not more than the area of the principal peak of paracetamol in the chromatogram obtained with reference solution (b) (0.3 per cent). The sum of areas of all the secondary peaks is not more than 6.66 times the area of the principal peak of paracetamol in the chromatogram obtained with reference solution (b) (2.0 per cent).

Indapamide. Page 2283

Related substances.
Reference solution (c). Delete the requirement.

Reference solution (d).
Change **from:** *Reference solution (d).*
to: *Reference solution (c).*

After chromatographic system, para 2, line 1
Change **from:** Inject reference solution (b) and (d).
to: Inject reference solution (b) and (c).

Labetalol Tablets. Page 2366

Related substances. Last para, line 1
Change **from**: 20 ml
to: 20 µl

Lapatinib Ditosylate. Page 2393

P-Toluenesulphonic acid.
Change **from**: Not less than 35.8 per cent w/w and not more than 37.2 per cent w/w.
to: Not less than 36.1 per cent w/w and not more than 38.0 per cent w/w, calculated on anhydrous basis.

Water. Line 1
Change **from**: 1.5 per cent to 2.3 per cent
to: Not more than 1.0 per cent

Lapatinib Tablets. Page 2394

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

Levodopa and Carbidopa Tablets. Page 2416

Insert the following, before **Uniformity of Content**.
Dissolution (2.5.2).
Apparatus No. 2,
Medium. 750 ml of *0.1 M hydrochloric acid,*

Speed and time. 50 rpm and 45 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.

Reference solution. A solution containing 0.005 per cent w/v of *levodopa RS* and 0.00054 per cent w/v of *carbidopa RS* in the dissolution medium.

Chromatographic system
- a stainless steel column 20 cm x 4.0 mm, packed with octylsilane bonded to porous silica (10 µm)(Such as Lichrosorb RP8),
- mobile phase: a *0.1 M potassium dihydrogen orthophosphate*, adjusted to pH 3.0 with *1 M orthophosphoric acid,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 282 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution.

Calculate the contents of $C_{10}H_{12}N_2O_4$ and $C_9H_{11}NO_4$ in the medium.

D. Not less than 75 per cent of the stated amounts of $C_{10}H_{12}N_2O_4$ and $C_9H_{11}NO_4$.

Levonorgestrel Tablets. Page 2428

Insert the following, before **Related substances**.
For tablets containing less than 100 µg of levonorgestrel—

Dissolution (2.5.2).

Apparatus No. 1,

Medium. 500 ml of *0.01 M hydrochloric acid,*
Speed and time.75 rpm and 30 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 0.1 per cent w/v solution of *sodium dodecylsulphate* in dissolution medium to produce a solution containing 0.000006 per cent w/v of levonorgestrel.

Reference solution. A 0.000006 per cent w/v solution of *levonorgestrel RS* in the dissolution medium.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS2),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water*,
- flow rate: 1.3 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 500 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{28}O_2$ in the medium.

D. Not less than 75 per cent of the stated amount of $C_{21}H_{28}O_2$.

For tablets containing 100 µg or more of levonorgestrel-

Apparatus No. 1,

Medium. 500 ml of 0.1 per cent w/v solution of *sodium lauryl sulphate* in *0.1 M hydrochloric acid,*
Speed and time.75 rpm and 30 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.

Reference solution. A 0.00015 per cent w/v solution of *levonorgestrel RS* in the dissolution medium.

Use chromatographic system as described under Dissolution (for tablets containing less than 100 µg of levonorgestrel) with the following modification.

- injection volume: 25 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{28}O_2$ in the medium.

D. Not less than 75 per cent of the stated amount of $C_{21}H_{28}O_2$.

Mefloquine Hydrochloride. Page 2512

Heavy metals. Line 2
Change **from**: Method C
to: Method B

Melphalan Tablets. Page 2520

Insert the following, before **Uniformity of Content**.

Dissolution (2.5.2).

Apparatus No. 2,
Medium. 900 ml of *0.1 M hydrochloric acid*,
Speed and time.100 rpm and 45 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 *0.1 M hydrochloric acid*.

Reference solution. Dilute a suitable volume of 0.1 per cent w/v solution of *melphalan RS* in a mixture of 4 volumes of *acetonitrile* and 1 volume of *0.1 M hydrochloric acid*, with sufficient *0.1 M hydrochloric acid* to produce a solution containing 0.0002 per cent w/v.

Chromatographic system

- a stainless steel column 20 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (10 µm) (Such as spherisorb ODS 1),
- mobile phase: a mixture of 200 volumes of 0.375 per cent w/v solution of *ammonium carbonate*,180 volumes of *methanol* and 2.7 volumes of *glacial acetic acid*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 100 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{18}Cl_2N_2O_2$ in the medium.

D. Not less than 75 per cent of the stated amount of $C_{13}H_{18}Cl_2N_2O_2$.

Memantine Tablets. Page 2522

Related substances. A.
After Chromatographic system, para 2, line 4
Change **from**: 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.15 per cent).
to: 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.3 per cent).

Line 11, insert at end.
…..excluding memantine lactose adduct.

B. After Chromatographic system, para 2, line 5

Change **from**: adduct is not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (0.5 per cent).

to: adduct is not more than 0.7 times the area of the principal peak in the chromatogram obtained with reference solution (1.4 per cent).

Metronidazole Injection. Page 2595

Identification A. Line 3

Change **from:** ….. further 5 minutes and evaporate to dryness.

to: …... further 5 minutes and allow to separate. Evaporate the upper layer to dryness.

Montelukast Sodium and Levocetirizine Hydrochloride Tablets. Page 2633

Dissolution. *Test solution*

Change **from**: Dilute the filtrate if necessary, with the *methanol*.

to: Dilute the filtrate if necessary, with the mobile phase A.

Reference solution (c), line 2

Change **from**: with dissolution medium

to: with mobile phase A.

Uniformity of content.

Change **to**: **Uniformity of content**. Complies with the test stated under Tablets.

Determine by liquid chromatography (2.4.14), using the chromatographic system and reference solution (c) as described under Assay.

Test solution. Disperse one tablet in 100.0 ml of volumetric flask. Add 25 ml of solvent mixture and sonicate for about 10 minutes with intermittent shaking. Dilute to volume with solvent mixture, mix and centrifuge.

Inject reference solution (c) and the test solution.

Calculate the contents of $C_{35}H_{36}ClNO_3S$ and $C_{21}H_{25}N_2O_3Cl$, 2HCl in the tablet.

Nadifloxacin. Page 2681

Related substances. After chromatographic system, para 2, line 10

Change **from:** 0.01 per cent

to: 0.1 per cent

Olmesartan Medoxomil and Hydrochlorothiazide Tablets. Page 2777

Related substances.

Change **to**:

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 50 mg of hydrochlorothiazide in 160 ml of the mobile phase, with the aid of ultrasound for about 25 minutes and dilute to 200.0 ml with the mobile phase, centrifuge at 2500 rpm for 15 minutes. Dilute 5.0 ml of supernatant to 50.0 ml with the mobile phase.

Reference solution (a). A 0.05 per cent w/v solution of *olmesartan medoxomil RS* in the mobile phase.

Reference solution (b). A 0.07 per cent w/v solution of *hydrochlorothiazide RS* in the mobile phase.

Reference solution (c). Dilute 4.0 ml of reference solution (a) and 2.0 ml of reference solution (b) to 50.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (such as Inertsil ODS-3),
- mobile phase: a mixture of 60 volumes of buffer solution prepared by dissolving 1 ml of *triethylamine* in 1000 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid* and 40 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 226 nm,
- injection volume: 20 µl.

The retention time of hydrochlorothiazide peak is about 4.2 minutes and olmesartan medoxomil is about 15 minutes.

Inject reference solution (c). The test is not valid unless the column efficiency is not less than 3000 theoretical plates, the tailing factor is not more than 2.0 and relative standard deviation for replicate injections is not more than 2.0 per cent for both the peaks.

Inject the test solution. The area of any secondary peak is not more than 1.0 per cent and the sum of areas of all the secondary peaks is not more than 2.0 per cent, calculated by area normalization.

Oxaliplatin. Page 2807

Related substances. C. Line 1
Change **from**: *Oxaliplatin Related Compound C*
to: *Oxaliplatin Related Compound D*

Reference solution (b).
Change **from**: Dilute 5.0 ml of reference solution (a) to 20.0 ml with *water.*
to: Dilute reference solution (a) with *methanol* to obtain a 0.0015 per cent w/v solution of oxaliplatin related compound D.

Reference solution (f). Line 3
Change **from**: reference solution (a)
to: reference solution (b)

Oxaliplatin Injection.Page 2810

Oxalic acid. *Test solution*
Change **from**: 0.5 per cent v/v
to: 0.2 per cent v/v

Last para, line 4
Change **from**: 0.85 times
to: 0.34 times

Related substances. *Test solution*
Change **from**: 0.5 per cent v/v
to: 0.2 per cent v/v

Last para, line 4
Change **from**: *N,N'*]platinum is not more than the area of the principal peak
to: *N,N'*]platinum is not more than 0.42 times the area of the principal peak

Line 7
Change **from**: 0.8 times
to: 0.32 times
Line 10
Change **from**: 0.32
to: 0.13
Line 15

Change **from**: 3.92 times
to: 1.57 times

Oxprenolol Tablets. Page 2817

Identification. D
Delete the requirement

Pantoprazole Gastro-resistant and Domperidone Prolonged-release Capsules. Page 2850

Dissolution. *For Pantoprazole sodium-*
Para1, lines 2 and 3
Delete. "*inject samples within 10 minutes of preparation*".

Pemetrexed Disodium Heptahydrate. Page 2870

Related substances. Delete from table

Name	Relative retention time
Pemetrexed impurity E[5]	0.94

[5]*(2R)*-2-[[4-[2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-*d*]pyrmidin-5y1)ethyl]benzoyljaminol]-pentanedioic acid.

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

Pemetrexed Injection. Page 2872

Related substances. Last para, line 2
Change **from**: ketopemetrexed
to: ketopemetrexed (correction factor 1.64),

Phytomenadione. Page 2925

Z-isomer content
Change **from**:

$$= \frac{tz_X 100}{tz - te}$$

to:

$$= \frac{tz_X 100}{tz + te}$$

Pindolol. Page 2931

Heavy metals. Line 2
Change **from**: Method C
to: Method B

Pitavastatin Calcium. Page 2951

Related substances. Chromatographic system. Mobile phase, line 2
Change **from**: 40 volumes
to: 585 volumes

Polyethylene Glycol 4000. Page 2955

Hydroxyl value.

Change **from**: 30 to 36, determined on 20.0 g.
to: 30 to 36, determined on 2.0 g.

Pravastatin Sodium. Page 2973

Ethanol.
Change **from**: Not more than 3.0 per cent v/v (determined by method I).
to: Not more than 3.0 per cent (determined by method I).

Prochlorperazine Mesylate. Page 3006

Identification. B, last line
Change **from**: ...absorbance at about 258 nm, about 0.6.
to: ...absorbance at about 258 nm, about 0.63.

Assay. Line 6
Change **from**: ....2 ml of *ethanol*, evaporate to dryness.
to: ....2 ml of *ethanol*, evaporate to dryness. Dissolve the residue in 50 ml of *anhydrous glacial acetic acid.*

Promethazine Theoclate. Page 3017

Identification. A. Para 2, lines 2 and 3
Change **from**: Compare the spectrum with that obtained with *promethazine RS* or with the reference spectrum of promethazine.
to: Compare the spectrum with that obtained with *promethazine theoclate RS* treated in the same manner or with the reference spectrum of promethazine.

Propofol. Page 3020

Related substances. After Chromatographic system, para 1, line 5
Change **from**: propofol impurity G
to: propofol impurity I

Line 8
Change **from**: propofol impurity F
to: propofol impurity N

Rebamipide. Page 3100

Heavy metals. Line 2
Change **from**: Method A
to: Method B

Chloride (2.3.12).
Change **from**: Dissolve 1.0 g in 15 ml of *water*, the solution complies with the limit test for chlorides (250 ppm).
to: Shake 1.0 g with 40 ml of *water* for 5 minutes and filter. The filtrate complies with the limit test for chlorides (250 ppm).

Repaglinide and Metformin Tablets. Page 3104

Uniformity of Content

For Repaglinide
Test solution. Lines 2 and 4
Change **from:** solvent mixture
to: mobile phase

Reference solution. Line 2
Change **from:** solvent mixture
to: mobile phase

Riboflavin Sodim Phosphate. Page 3112

Identification. C, line 5
Change **from**: (2.4.1)
to: (2.3.1)

Colloidal Sodium Dioxide. Page 3188

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

Sodium Valproate Tablets. Page 3242

Insert the following, before **Related substances**

Dissolution (2.5.2).

Apparatus No. 1,
Medium. 900 ml of *phosphate buffer pH 6.8*,
Speed and time. 50 rpm and 45 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.

Reference solution. Dissolve a quantity of *sodium valproate RS* with the dissolution medium 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) (Such as µ bondapak C18),
- mobile phase: a mixture of 45 volumes of a buffer solution prepared by dissolving 0.32 g *potassium dihydrogen orthophosphate* in 100 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid* and 55 volumes of *acetonitrile*,
- 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.

D. Not less than 75 per cent of the stated amount of $C_8H_{15}NaO_2$.

Tacrolimus. Page 3295

Related substances. Last Para, line 21
Change **from**: Ignore any peak with area less than
to: Ignore any peak with area less than 0.05 times

Tamoxifen Tablets. Page 3305

Insert the following, before **E-Isomer and Related substances**.

Dissolution (2.5.2).

Apparatus No 2,
Medium.1000 ml of *0.02 M hydrochloric acid,*
Speed and time.150 rpm and 45 minutes.
Withdraw a suitable volume of the medium and filter, dilute if necessary with the dissolution medium. Measure the absorbance of the resulting solution at the maximum at about 275 nm (2.4.7). Calculate the content of $C_{26}H_{29}NO$ in the medium taking 305 as the specific absorbance at 275 nm.

D. Not less than 75 per cent of the stated amount of $C_{26}H_{29}NO$.

Tamsulosin Hydrochloride Prolonged-release and Dutasteride Capsules. Page 3309

Related substances.

For Dutasteride III and Isomer impurity-

After chromatographic system, para1

Change **from**: The relative retention time with respect to dusteride for dusteride III is about 0.69 and dusteride isomer is about 1.05.

to:

Name	Relative retention time
Dutasteride III[1]	0.69
Dutasteride Isomer[2]	1.05

[1]3-oxo-4-aza-5a-androst-1-ene-17β-carboxylic acid,

[2]17β-N-[2,5-bis(trifluoromethyl)phenyl]carbomoyl-4-aza-5β-androst-1 ene-3-one.

Para 3

Change **to**: Inject the test solution. The area of any peak corresponding to dutasteride III and dutasteride isomer is not more than 1.0 per cent, the area of any other secondary peak is not more than 1.0 per cent and the sum of areas of all the secondary peaks is not more than 2.0 per cent, calculated by area normalisation.

For Dutasteride dihydro impurity —

Chromatographic system, lines 1 and 2

Change **to**: a stainless steel column 25 cm x 4.6 mm, packed with porous silica (5 µm) (Such as kromasil 100 silica),

After chromatographic system, para1

Change **to**: The relative retention time with respect to dutasteride for dutasteridedihydro impurity (*17β-N-{2,5-bis(trifluoromethyl)phenyl}carbomoyl-4-aza-5a-androstane-3-one)*is about 1.98.

Para 3

Change **to**: Inject the test solution. The area of any peak corresponding to dutasteridedihydro impurity is not more than 1.0 per cent, the area of any other secondary peak is not more than 1.0 per cent and the sum of areas of all the secondary peaks is not more than 2.0 per cent, calculated by area normalisation.

Ticagrelor. Page 3374

Related substances. After chromatographic system, Ticagrelor impurity G[4]

Change **from**: [4](1S,2S, 3R,5S)-3-{7-[(1R*, 2S*)-2-(3,4-Difluorophenyl) cyclopropyl] amino]-5-(propylthio)-3H-[1,2,3] triazolo[4,-5d] pyrimidin-3-yl}-5-(2-hydroxyethoxy) cyclopentane-1,2-diol (* indicates mixture of diastereomers)

to: [4](1S*,2S*,3R,5S)-3-{7-[(1R, 2S)-2-(3,4-Difluorophenyl) cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,-5d] pyrimidin-3-yl}-5-(2-hydroxyethoxy) cyclopentane-1,2-diol (* indicates mixture of diastereomers).

Xylometazoline Nasal Drops. Page 3527

Assay

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

Test solution. Mix the contents of 10 containers. Transfer a suitable volume of the sample containing 10 mg of Xylometazoline Hydrochloride into 50 ml- volumetric flask and dilute to volume with the mobile phase and mix.

Reference solution. Dissolve 20 mg of *xylometazoline hydrochloride RS* in 10 ml of *methanol* and dilute to 100.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica(5 µm) (Such as hypersil),

- mobile phase: a mixture of 60 volumes of buffer solution prepared by dissolving 2.5 g of *anhydrous ammonium sulphate* in 1000 ml of *water*, adjust the pH 2.7 with 1M *orthophosphoric acid* and 40 volumes of *acetonitrile,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 20 µl.

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 $C_{16}H_{24}N_2$, HCl in the nasal drops.