INDIAN PHARMACOPOEIA COMMISSION

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Date: 29th July, 2020

To,

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

Subject: Amendment List-07 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-07 to IP 2018 is issued containing such amendments.

This is for notice and compliance with the IP 2018.

(Dr. Jai Prakash) 29/07/2020
Secretary-cum-Scientific Director (I/c)

Encl. Amendment List-07 to IP 2018

Amendment List 07 to IP-2018

2.4.26. Solubility. Page 220

Insert before **Abacavir Sulphate**

The term 'partly soluble' is used to describe a mixture where only some of the components dissolve. The term 'miscible' is used to describe a liquid that is miscible in all proportions with the stated solvent.

Tablets. Page 1118

Gastro-resistant Tablets. Page 1120

Disintegration. Line 9 and 10

Change **from**: *mixed phosphate buffer pH 6.8*

to: *phosphate buffer pH 6.8*

Baclofen. Page 1321

Insert after **Identification**

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.

Bisacodyl Gastro-resistant Tablets. Page 1390

Related substances

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

Solvent mixture. 4 volumes of *glacial acetic acid*, 30 volumes of *acetonitrile* and 66 volumes of *water*.

Test solution. Shake a quantity of the powdered tablets containing about 25 mg of Bisacodyl with 40 ml of the solvent mixture and dilute to 50.0 ml with the same solvent, filter.

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 reference solution (a) to 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with base deactivated octadecylsilane bonded to porous silica (5μm),
- mobile phase: a mixture of 45 volumes of *acetonitrile* and 55 volumes of *0.025 M ammonium formate*, previously adjusted to pH 5.0 with *anhydrous formic acid*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 265 nm,
- injection volume: 50 µl

Name	Relative retention time	Correction factor
Bisacodyl impurity A[1]	0.2	0.7
Bisacodyl impurity B[2]	0.4	-
Bisacodyl impurity C[3]	0.45	-
Bisacodyl impurity D[4]	0.8	-
Bisacodyl impurity E[5]	0.9	-
Bisacodyl (Retention time : about 13 minutes)	1.0	-
Bisacodyl impurity F[6]	2.6	-

[1]4,4′-(pyridin-2-ylmethylene)diphenol
[2]2-[(RS)-(4-hydroxyphenyl)(pyridin-2-yl)methyl]phenol,
[3]4-[(RS)-(4-hydroxyphenyl)(pyridin-2-yl)methyl]phenyl acetate,
[4, 6]unknown structure.
[5]2-[(RS)-[4-(acetyloxy) phenyl](pyridin-2-yl)methyl]phenyl acetate,

Inject reference solution (a), (b) and the test solution. Run the chromatogram 3.5 times of the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any secondary peak corresponding to bisacodyl impurity C 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), the area of any secondary peak corresponding to bisacodyl impurity A is not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent), the area of any secondary peak corresponding to bisacodyl impurity E is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any secondary peak corresponding to bisacodyl impurity F 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 secondary peak corresponding to bisacodyl impurity D 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 other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of areas of all the secondary peaks excluding bisacodyl impurity A and C is not more than 5 times of the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 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).

Isopropyl Rubbing Alcohol. Page 2328

Para 1

Change **from:** Isopropyl Rubbing Alcohol contains not less than 68.0 per cent and not more than 72.0 per cent of isopropyl alcohol.

to: Isopropyl Rubbing Alcohol contains not less than 68.0 per cent v/v and not more than 72.0 per cent v/v of isopropyl alcohol, C_3H_8O with the remainder consisting of water, with or without suitable stabilizers, perfume oil and colour permitted for the use in drugs.

Specific gravity

Change **from:** 0.872 to 0.883 at 25°.

to: 0.872 to 0.883 at 20°.

Assay

Change **from:** Transfer 50.0 ml to a 250-m1 distilling flask and add 100 ml of *water*. Distil and collect 95 ml of distillate and dilute to 100 ml with *water* and determine the specific gravity (2.4.29) at 25°. The specific gravity is 0.955 to 0.950, corresponding to 68 per cent and 72 per cent of isopropyl alcohol in the specimen taken.

to: Determine by gas chromatography (2.4.13).

Internal standard solution . A 0.7 per cent v/v solution of *1-propanol* in *water*.

Test solution. Dilute 1.0 ml of the solution under examination to 100.0 ml with internal standard solution.

Reference solution. A 0.7 per cent v/v solution of *isopropyl alcohol* in internal standard solution.

Chromatography system

- a capillary column 30 m x 0.25 mm, packed with 6.0 per cent polycyanopropylphenyldimethyl siloxane and 94 per cent of polydimethyl siloxane (film thickness 1. 4 µm) (Such as DB-624),
- temperature:
- column 50° for 2 minutes, 50° to 240° @ 20° per minute and hold at 240° for 2 minutes,
- inlet port 180° and detector at 280°,
- flame ionization detector,
- split ratio: 25:1,
- flow rate 0.5 ml per minutes, using nitrogen as carrier gas,
- injection volume: 1 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to isopropyl alcohol and 1-propanol is not less than 2.0 and the relative standard deviation of peak area ratio due to isopropyl alcohol and internal standard for the replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of C_3H_8O.

Storage
Change from: Store protected from heat and moisture.
to: Store protected from heat and preserve in tight containers.

Lignocaine Hydrochloride Topical Solution. Page 2437

Storage
Change **from:** Store protected from moisture.
to: Store at a temperature not exceeding 30˚.

Ormeloxifene Hydrochloride. Page 2794

Identification
Change **to:**
A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ormeloxifene hydrochloride RS* or with the reference spectrum of ormeloxifene hydrochloride.

B. When examined in the range 230 nm to 360 nm (2.4.7), a 0.01 per cent w/v solution in *methanol* shows absorption maxima at about 278 and 282 nm.

C. 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.

Insert before **cis-Isomer**
Related substances. Determine by liquid chromatography (2.4.14).
Solvent mixture. 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Test solution. Dissolve 40 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the same solvent.

Reference solution. A 0.0004 per cent w/v solution of *ormeloxifene hydrochloride RS* in the solvent mixture.

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 3V),
- mobile phase: A. buffer solution pH 2.5 prepared by dissolving 0.63 g of *ammonium formate* in 1000 ml of *water*, add 2 ml of *triethylamine*, adjusted to pH 2.5 with *formic acid*,
B. a mixture of 20 volumes of *acetonitrile* and 80 volumes of *methanol*,
- a gradient programme using the conditions given blow,
- 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	40	60
20	30	70
40	30	70
42	40	60
55	40	60

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent.

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 0.6 times the area of the principal peak in the chromatogram obtained with the reference solution (0.3 per cent) and 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 (1.0 per cent). Ignore the peak due to cis-isomer at relative retention time of about 0.9 and 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).

D- Panthenol. Page 2847

Specific optical rotation

Change **from:** + 28.2° to + 30.2°, determined at 20° in a 5.0 per cent w/v solution.

to: +29.0° to + 31.5°, determined in a 5.0 per cent w/v solution.

Propofol. Page 3020

Impurities J, K, L and O, chromatographic system, line 4

Change **from:** $80^o - 120^o$

to: $80^o - 210^o$

Ropinirole Prolonged-release Tablets. Page 4501

Para 2, line 3

Change **from:** $C_{18}H_{24}N_4O$

to: $C_{16}H_{24}N_2O$

Ropinirole Tablets. Page 4502

Para 1, line 3

Change **from:** $C_{18}H_{24}N_4O$

to: $C_{16}H_{24}N_2O$

Serratiopeptidase Tablets. Page3181

Assay. Last para

Change **to:**

$$\text{Serratiopeptidase Units/Tablet} = \frac{A_1 - A_2}{A_3 - A_4} \times 176 \times \frac{T}{0.160} \times \frac{1}{20} \times \frac{100}{\text{Spl. Wt. (gm)}} \times \frac{25}{5} \times \frac{100}{2} \times \text{Avg. wt. in gm}$$

$$\%\ \text{of L. A.} = \frac{\text{Serratiopeptidase Units/Tablet}}{\text{L. A.}} \times 100$$

Where, 176 = Conversion Co-efficient of Tyrosine to Serratiopeptidase

T = Actual weight of Tyrosine taken (gm)

0.160 = Theoretical weight of Tyrosine to be taken

20 = Reaction time [minutes]

A1 = Absorbance of test solution

A2 = Absorbance of blank solution

A3 = Absorbance of tyrosine reference solution)

A4 = Absorbance of 0.2M hydrochloric acid)

L.A. = Labelled amount/tablet.

Sodium Propylparaben. Page 3233

Related substances. After chromatographic system, para 2, line 3

Change **from:** 5.0

to: 3.0

Teneligliptin Hydrobromide Hydrate. Page 4521

Water

Change **from:** 4.0 per cent to 6.0 per cent, determined on 0.25 g.

to: 2.8 per cent to 6.0 per cent, determined on 0.25 g.

Thiocolchicoside. Page 3357

Related substances. After chromatographic system, para 1, line 2

Change **from:** 80000

to: 20000

Ticagrelor. Page 3374

Related substances

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

NOTE—Carry out the test protected from light.

Solvent mixture. 35 volumes of *acetonitrile* and 65 volumes of *water*.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.005 per cent w/v solution of *ticagrelor RS* in the solvent mixture. Dilute 1.0 of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.05 per cent w/v of *ticagrelor RS* and 0.0001 per cent w/v of *ticagrelor impurity B RS* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 3.0 mm packed with phenyl group bonded to porous silica (3 µm),
- column temperature: 40º,
- mobile phase: A. a mixture of 89 volumes of *water*, 10 volumes of *acetonitrile* and 1 volume of a buffer solution,
  B. a mixture of 29 volumes of *water*, 70 volumes of *acetonitrile* and 1 volume of a buffer solution,
- a gradient programme using the conditions given below,
- flow rate: 0.65 ml per minute,
- spectrophotometer set at 242 nm,
- injection volume: 5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
2	80	20
42	25	75
47	25	75
47.1	80	20
50	80	20

Name	Relative retention time	Correction factor
Ticagrelor impurity A [1]	0.15	0.5
Ticagrelor	1.0	-
Ticagrelor impurity B [2]	1.06	-
Ticagrelor impurity C [3]	1.23	-
Ticagrelor impurity D [4]	1.49	-

[1] (1S,2S,3R,5S)-3-{7-amino-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}-5-(2-hydroxyethoxy)cyclopentane-1,2-diol,

[2] (1S,2S,3R,5S)-3-({3-[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl}amino)-5-(2-hydroxyethoxy) cyclopentane-1,2-diol,

[3] 2-{[(1S,2S,3S,4R)-4-(7-{[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,3-dihydroxycyclopentyl]oxy}ethyl acetate,

[4] 2-{[(3aR,4S,6R,6aS)-6-(7-{[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl]oxy}ethanol.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to ticagrelor and ticagrelor impurity B is not less than 4.0.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to ticagrelor impurity A and impurity B, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to ticagrelor impurity C is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any peak corresponding to ticagrelor impurity D is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 10 times 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 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulphated ash

Change **to**: **Sulphated ash** (2.3.18). Not more than 0.6 per cent, using platinum crucible.

Titanium Dioxide. Page 3383

Assay. Last para, last line
Change **from**: Solution A
to: Solution B

Tobramycin Inhalation Solution. Page 3388

Related substances. *Reference solution (e)*, line 2
Change **from:** reference solution (a)
to: reference solution (d)

Torsemide Tablets. Page 340

Related substances. Chromatographic system, mobile phase
Change **to:** mix 45 volumes of solution containing 10 volumes of *acetonitrile* and 90 volumes of *methanol* and 55 volumes of a buffer solution prepared by dissolving 2.72 g of *monobasic potassium phosphate* in 1000 ml of *water* and adjust to pH 4.0 with *orthophosphoric acid*,

Yellow Fever Vaccine. Page 3714

SEED LOT. Para 2, line 2
Change **from:** 204 and 239
to: 204 and 240