INDIAN PHARMACOPOEIA COMMISSION

(Ministry of Health & Family Welfare, Government of India)
Sector 23, Raj Nagar, Ghaziabad 201002 (U.P.), India
E-mail: lab.ipc@gov.in; Website: www.ipc.gov.in

IP Reference Substances and their use in Drug Testing

Dr Robin Kumar

Principal Scientific Officer

Indian Pharmacopoeia Reference Substances (IPRS)

IPRS is a Primary Reference Substance that has the appropriate quality within a specified context and is accepted without requiring comparison to another substance.

Indian Pharmacopoeia Reference Standards (IPRS) are the authentic specimens chosen and verified on the basis of their suitability for intended use as prescribed in the IP.

Legal Status of IPRS

- IP is published by the IPC to fulfill the requirements of the Second Schedule of the Drugs and Cosmetics Act 1940 and Rules there under.
- IPRS are authoritative standards for determining the quality of medicines in India.

Drugs and Cosmetics Act, 1940

Class of drug	Standard to be complied with
1	2
[1][5. Other drugs: (*a*) Drugs included in the Indian Pharmacopoeia	Standards of identity, purity and strength specified in the edition of the Indian Pharmacopoeia for the time being in force and such other standards as may be prescribed. In case the standards of identity, purity and strength for drugs are not specified in the edition of the Indian Pharmacopoeia for the time being in force but are specified in the edition of the Indian pharmacopoeia immediately preceding, the standards of identity, purity and strength shall be those occurring in such immediately preceding edition of the Indian Pharmacopoeia and such other standards as may be prescribed.

Second Schedule of the Drugs and Cosmetics act 1940

IP Reference Substances (IPRS)

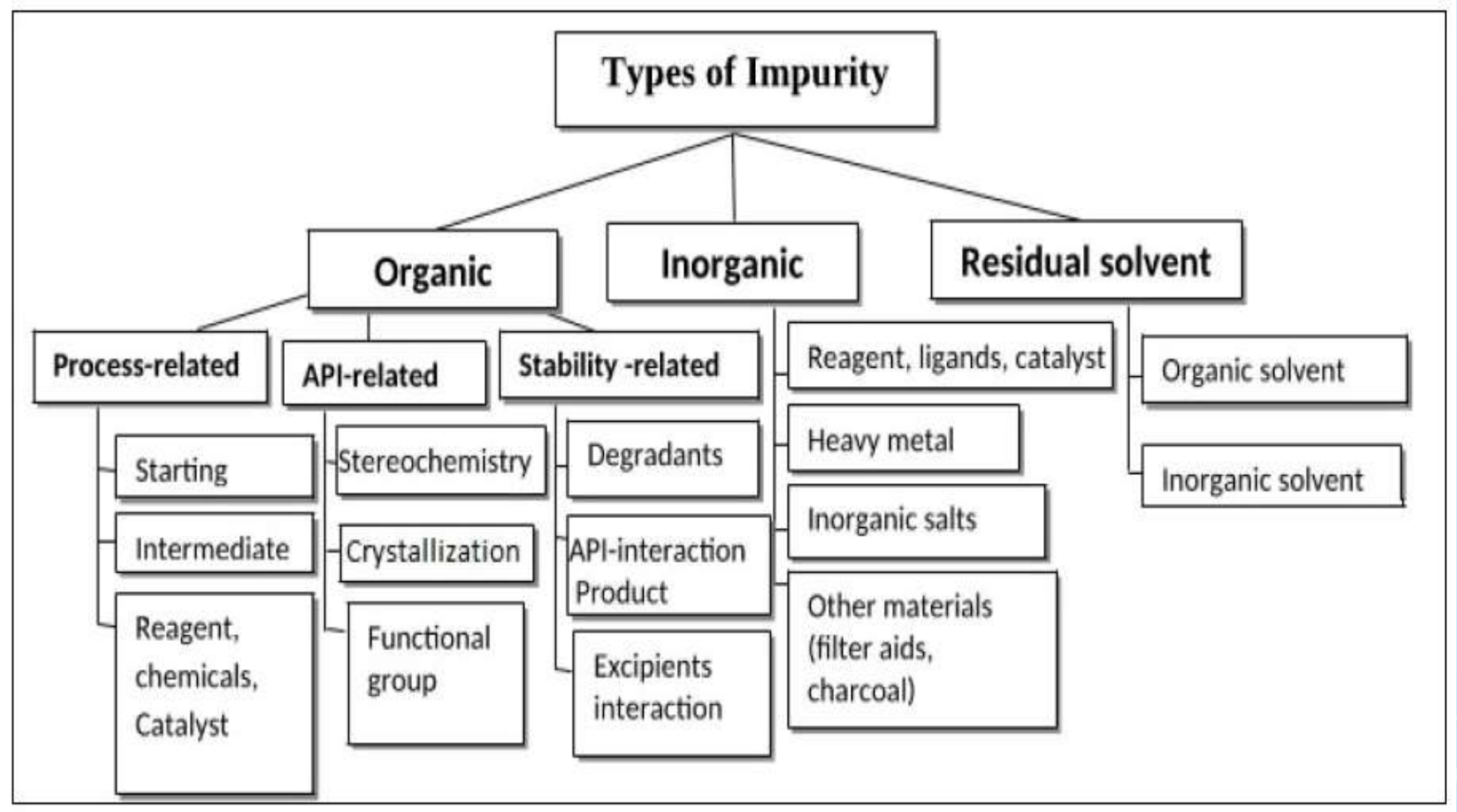
Indian Pharmacopoeia Reference Substances abbreviated, as IPRS in the individual monographs, are issued by the Indian Pharmacopoeia Commission (IPC) or by laboratories authorized by the IPC and assume the official status in India. Where an IPRS is referred to in an official IP monograph, it becomes a part of the official standard that is alone authoritative in case of doubt or dispute to determine compliance with the IP.

Legal Notices

In India, under the Drugs and Cosmetics Act 1940, the current edition of Indian Pharmacopoeia is a book of standards for drugs included therein and the standards as included in the Indian Pharmacopoeia would be official. Also, in several other laws of India, the Indian Pharmacopoeia is recognised as the standard book. It is expedient that enquiry be made in each

Various use of IPRS

Qualitative	Identification (IR), peak identification (By HPLC,GC,UV)
Quantitative	Assay, related substances, Dissolution and Content Uniformity
System Suitability	Resolution, S/N Ratio, peak to valley, theoretical plates, tailing factor, RSD, RRT
Verification/Calibration	Performance Verification Test for Dissolution Apparatus


Types of Impurity
Organic
Inorganic
Residual solvent
Process-related
API-related
Stability -related
Starting
Intermediate
Reagent, chemicals, Catalyst
Stereochemistry
Crystallization
Functional group
Degradants
API-interaction Product
Excipients interaction
Reagent, ligands, catalyst
Heavy metal
Inorganic salts
Other materials (filter aids, charcoal)
Organic solvent
Inorganic solvent

IPRS in Identification

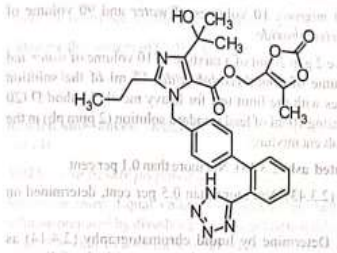
Congealing point. Dry about 10 ml by heating to 110° with frequent stirring, transfer to a test-tube about 20 mm in diameter, cool and when at 15° immerse the tube in a suitable water-bath so that the cooling takes place at the rate of 2° per minute. Stir the sample with a thermometer; it does not become cloudy until the temperature has fallen to 10°. On further cooling it congeals to a white solid or semi-solid mass at about 4°.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Storage. Store protected from light and moisture in a refrigerator (8° to 15°).

Labelling. The label states the name and concentration of any added antioxidant.

Olmesartan Medoxomil



$C_{29}H_{30}N_6O_6$ Mol.Wt. 558.6

Olmesartan Medoxomil is (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate.

Olmesartan Medoxomil contains not less than 97.5 per cent and not more than 102.0 per cent of $C_{29}H_{30}N_6O_6$, calculated on the anhydrous basis.

Category. Antihypertensive.

Production

As Nitrosamines are classified as probable human carcinogens, their presence in olmesartan medoxomil should be avoided or limited as much as possible. For this reason, manufacturers of olmesartan medoxomil for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in olmesartan medoxomil. The general chapter 5.11. Nitrosamine Impurities is available to assist manufacturers.

Description. A white or almost white, crystalline powder.

Identification

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *olmesartan medoxomil IPRS* or with the reference spectrum of olmesartan medoxomil.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Test solution (a). Dissolve about 25 mg of the substance under examination in *acetonitrile* and dilute to 25.0 ml with *acetonitrile*.

Test solution (b). Dissolve 25 mg of the substance under examination in *acetonitrile* and dilute to 50.0 ml with *acetonitrile*.

Reference solution (a). Dilute 1.0 ml of test solution (a) to 50.0 ml with *acetonitrile*. Dilute 1.0 ml of the solution to 10.0 ml with *acetonitrile*.

Reference solution (b). A 0.05 per cent w/v solution of *olmesartan medoxomil IPRS* in *acetonitrile*.

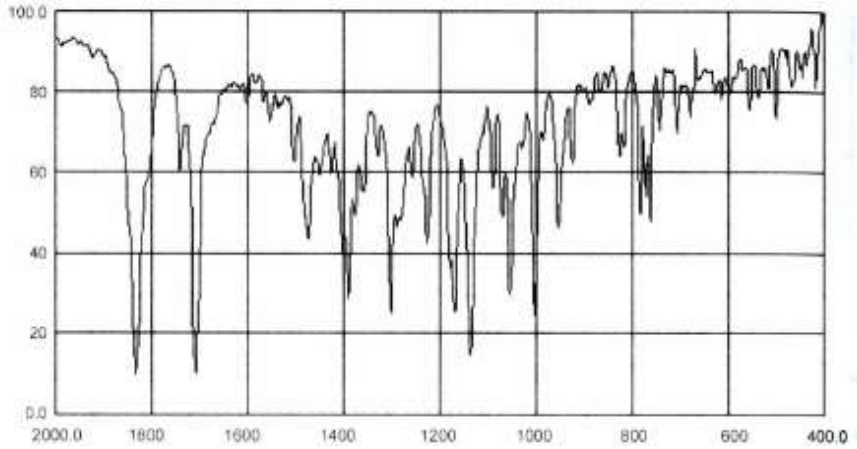
Chromatographic system

- a stainless steel column 10 cm x 4.6 mm packed with octylsilane bonded to porous silica (3.5 µm),
- column temperature: 40°,
- mobile phase: A. a mixture 80 volumes of buffer solution prepared by dissolving 2.04 g of *potassium dihydrogen orthophosphate* in 1000 ml *water*, adjusted to pH 3.4 with *orthophosphoric acid* and 20 volumes of *acetonitrile*,

  B. a mixture of 20 volumes of buffer solution and 80 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
10	75	25
35	0	100
45	0	100
48	75	25

Olmesartan Medoxomil *FTIR* Phase: KBr disc



IPRS in RS/Assay Testing as per IP

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). 4.7 to 6.7 per cent, determined on 0.2 g.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh accurately about 50 mg of the substance under examination and dissolve in 100.0 ml of *water*.

Reference solution (a). A 0.05 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in *water*.

Reference solution (b). A 0.05 per cent w/v solution of *ciprofloxacin ethylenediamine analog IPRS* in *reference solution (a)*.

Chromatographic system
- a stainless steel column 25 cm x 4 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 87 volumes of *0.025 M phosphoric acid*, previously adjusted to pH 3.0 ± 0.1 with *triethylamine* and 13 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- column temperature: 30° ± 1°,
- spectrophotometer set at 278 nm,
- injection volume: 10 µl.

Inject reference solution (b) and record the chromatogram adjusting the sensitivity and flow rate suitably so that the retention time for ciprofloxacin is between 6.4 and 10.8 minutes, the relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin and the resolution between ciprofloxacin ethylenediamine analog peak and ciprofloxacin peak is not less than 6.

Inject reference solution (a). The test is not valid unless the column efficiency, determined from ciprofloxacin peak, is not less than 2500 theoretical plates, the tailing factor for the ciprofloxacin peak is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.5 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{18}FN_3O_3,HCl$.

Storage. Store protected from light.

Ciprofloxacin Eye Drops

Ciprofloxacin Hydrochloride Eye Drops

Ciprofloxacin Eye Drops are a sterile solution of Ciprofloxacin Hydrochloride in Purified water.

Ciprofloxacin Eye Drops contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of ciprofloxacin, $C_{17}H_{18}FN_3O_3$.

Usual strength. 0.3 per cent w/v.

Identification

A. 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 (a).

B. It give reaction (A) of chlorides (2.3.1).

Tests

pH (2.4.24). 3.5 to 5.5.

Other tests. Comply with the tests stated under Eye Drops.

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Transfer an accurately measured volume of Eye drops containing 6 mg of ciprofloxacin, to a 50-ml volumetric flask, dilute with *water* to volume, and mix.

Reference solution (a). A 0.014 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in *water*.

Reference solution (b). A 0.001 per cent w/v solution of *ciprofloxacin ethylenediamine analog IPRS* in *reference solution (a)*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 30°,
- mobile phase: a mixture of 75 volumes of *0.005 M tetrabutylammonium phosphate*, adjusted to pH 2.0 with *orthophosphoric acid* and 25 volumes of *methanol*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (b). The relative retention time are about 0.8 for the ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin and the resolution between the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak is not less than 1.5.

Inject reference solution (a). The test is not valid unless the column efficiency is not less than 500 theoretical plates, the tailing factor not more than 2.0, and the relative standard deviation for replicate injections is not more than 2 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{18}FN_3O_3$ in the eye drops.

Storage. Store protected from light.

Ciprofloxacin Tablets

Ciprofloxacin Hydrochloride Tablets

Ciprofloxacin Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of

Paracetamol

Identification

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

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

B. Dissolve 50 mg in sufficient *methanol* to produce 100 ml. To 1 ml of the solution add 0.5 ml of *0.1 M hydrochloric acid* and dilute to 100 ml with *methanol*. Protect the resulting solution from bright light and immediately measure the absorbance at the maximum at about 249 nm; absorbance at 249 nm, about 0.44 (2.4.7).

C. Boil 0.1 g in 1 ml of *hydrochloric acid* for 3 minutes, add 10 ml of *water* and cool; no precipitate is produced. Add 0.05 ml of *0.0167 M potassium dichromate*; a violet colour develops which does not turn red.

D. It gives the reaction of acetyl groups (2.3.1).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Note—Prepare the solutions immediately before use.

Test solution. Dissolve 0.2 g of the substance under examination in 2.5 ml of *methanol* containing 0.46 per cent w/v of *tetrabutylammonium hydroxide solution* (40 per cent w/v) and dilute to 10.0 ml with the solution containing equal volumes of 1.79 per cent w/v of *disodium hydrogen phosphate* and 0.78 per cent w/v of *sodium dihydrogen phosphate*.

Reference solution (a). Dilute 1.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 5.0 ml of the solution to 100.0 ml with the mobile phase.

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

Reference solution (c). A solution containing 0.025 per cent w/v each of *4-aminophenol IPRS*, *paracetamol IPRS* and *chloroacetanilide IPRS* in *methanol*. Dilute 1.0 ml of the solution to 250.0 ml with the mobile phase.

Reference solution (d). Dissolve 20 mg of *4-nitrophenol IPRS* in 50.0 ml of *methanol*. Dilute 1.0 ml of the solution to 20.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5µm) (Such as Zorbax C8),
- column temperature: 35°,
- mobile phase: a mixture of 37.5 volumes of a 1.79 per cent w/v solution of *disodium hydrogen phosphate*, 37.5 volumes of a 0.78 per cent w/v solution of *sodium dihydrogen phosphate* and 25 volumes of *methanol* containing 0.46 per cent v/v of *tetrabutylammonium hydroxide solution (40 per cent w/v)*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 245 nm,
- injection volume: 20 µl.

The relative retention time with reference to paracetamol for 4-aminophenol is about 0.8, for 4-nitrophenol is about 3.0 and for chloroacetanilide is about 7.0.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to 4-aminophenol and paracetamol is not less than 4.0 and the signal-to-noise ratio of the peak due to chloroacetanilide is not less than 50.

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

Heavy metals (2.3.13). 2.0 g complies with the limit test for heavy metals, Method B (10 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°.

Assay. Dissolve 0.5 g in a mixture of 10 ml of *water* and 50 ml of *1 M sulphuric acid*. Boil under a reflux condenser for 1 hour, cool and dilute to 100.0 ml with *water*. To 20.0 ml of the solution add 40 ml of *water*, 40 g of *water* in the form of ice, 15 ml of *2 M hydrochloric acid* and 0.1 ml of *ferroin solution* and titrate with *0.1 M ceric ammonium sulphate* until a yellow colour is produced. Carry out a blank titration.

1 ml of *0.1 M ceric ammonium sulphate* is equivalent to 0.00756 g of $C_8H_9NO_2$.

Storage. Store protected from light and moisture.

IPRS for Calibration/Verification

- **IP Prednisone Dissolution Calibrator Tablet (IPRSP007)** is available at IPC which is recommended to verify the performance of Dissolution apparatus.
- **Caffeine (IPRSC050)** is available at IPC which is recommended to use in Calibration of HPLC.
- **Nicotinic Acid (IPRSN018)** is also developed by IPC and is mentioned in IP 2022 for use in calibration of UV.

Case Study 1: Development of Nicotinic Acid RS for Calibration in UV

IP is the only Pharmacopoeia in the globe who is providing below table/ values associated with the use of Nicotinic Acid for Calibration of UV

Table

Wavelength (nm)	Specific absorbance A (1 per cent, 1 cm)	Maximum Tolerance
213	424.4	419.4 to 429.3
235	124.5	122.9 to 126.2
257	144.5	142.8 to 146.2
261	419.2	412.0 to 423.9
313	48.6	47.0 to 50.3
350	107.3	105.6 to 109.0
430	15.9	15.7 to 16.1

Case Study 2 (Cyanocobalamin): Working standard Vs IPRS

Assay. Weigh accurately about 25 mg and dissolve in sufficient *water* to produce 1000.0 ml. Measure the absorbance of the solution at the maximum at about 361 nm (2.4.7). Calculate the content of $C_{63}H_{88}CoN_{14}O_{14}P$ taking 207 as the specific absorbance at 361 nm.

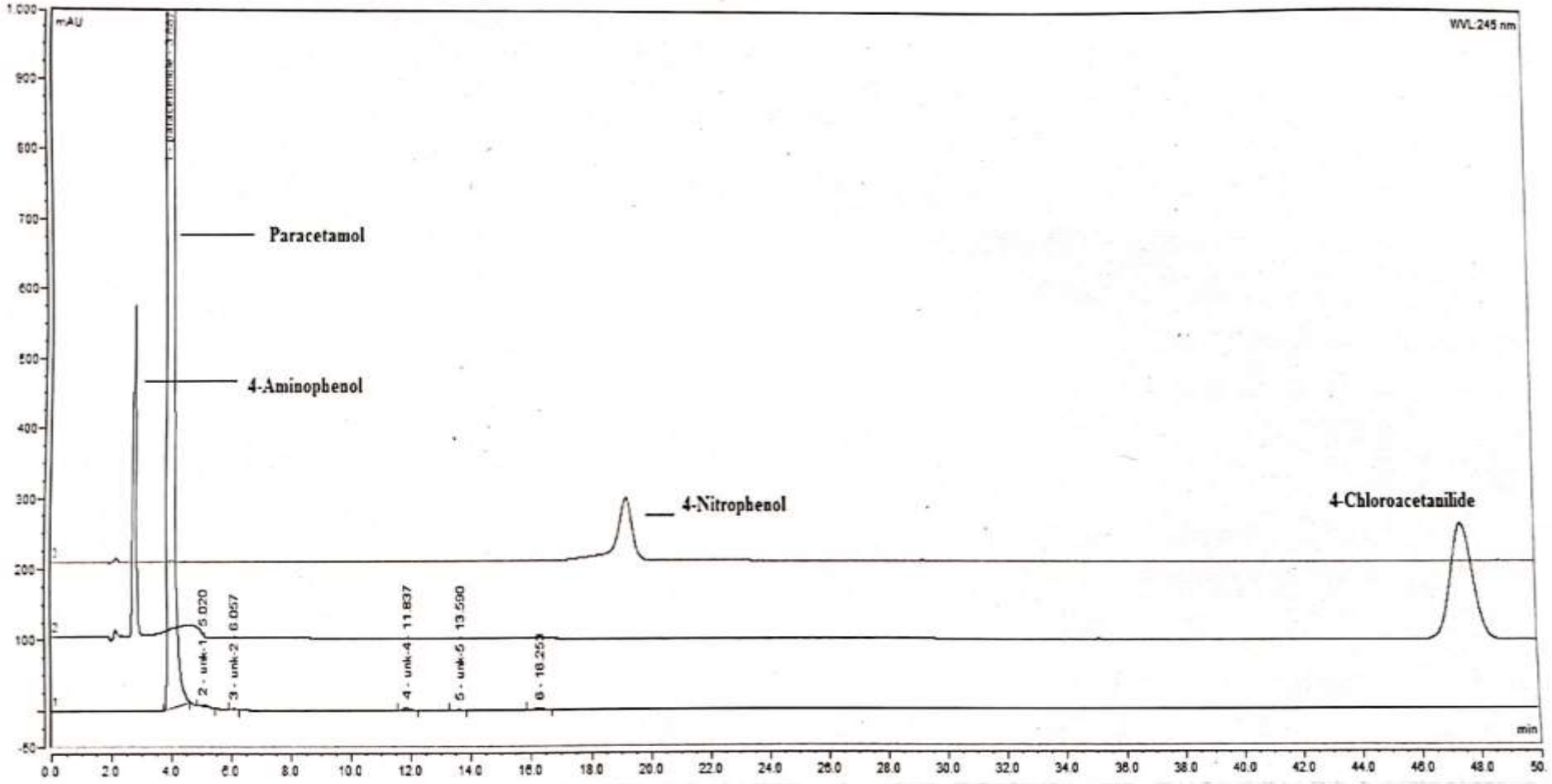
- In case of Cyanocobalamin the working standard purity determined by doing Assay by UV.
- Whereas, the Purity of Cyanocobalamin IPRS is determined by Liquid chromatography.

Case Study 3 (Paracetamol): Working standard Vs IPRS

Assay. Dissolve 0.5 g in a mixture of 10 ml of *water* and 50 ml of *1 M sulphuric acid*. Boil under a reflux condenser for 1 hour, cool and dilute to 100.0 ml with *water*. To 20.0 ml of the solution add 40 ml of *water*, 40 g of *water* in the form of ice, 15 ml of *2 M hydrochloric acid* and 0.1 ml of *ferroin solution* and titrate with *0.1 M ceric ammonium sulphate* until a yellow colour is produced. Carry out a blank titration.

1 ml of *0.1 M ceric ammonium sulphate* is equivalent to 0.00756 g of $C_8H_9NO_2$.

- In case of Paracetamol the working standard purity determined by doing Assay by Titration.
- While, the Purity of Paracetamol (IPRS) is determined by Liquid chromatography.


mAU
WVL:245 nm
Paracetamol
4-Aminophenol
4-Nitrophenol
4-Chloroacetanilide
2 - unk-1 5.020
3 - unk-2 6.057
4 - unk-4 11.837
5 - unk-5 13.590
6 - 16.253
min

IPRS Development Process Flow

Candidate material received

Preparation & approval of test protocol

Sampling as per designed protocol

Candidate material to concerned laboratories for testing

Lab-1 (IPL)

Lab-2

Lab-3

Lab-4

Analysis of candidate material

Data evaluation by Quality Control Laboratory Head

Review of data by Quality Assurance

Final approval of Results of Analysis

Filling, labeling & Final check of IPRS

Ready to Dispatch

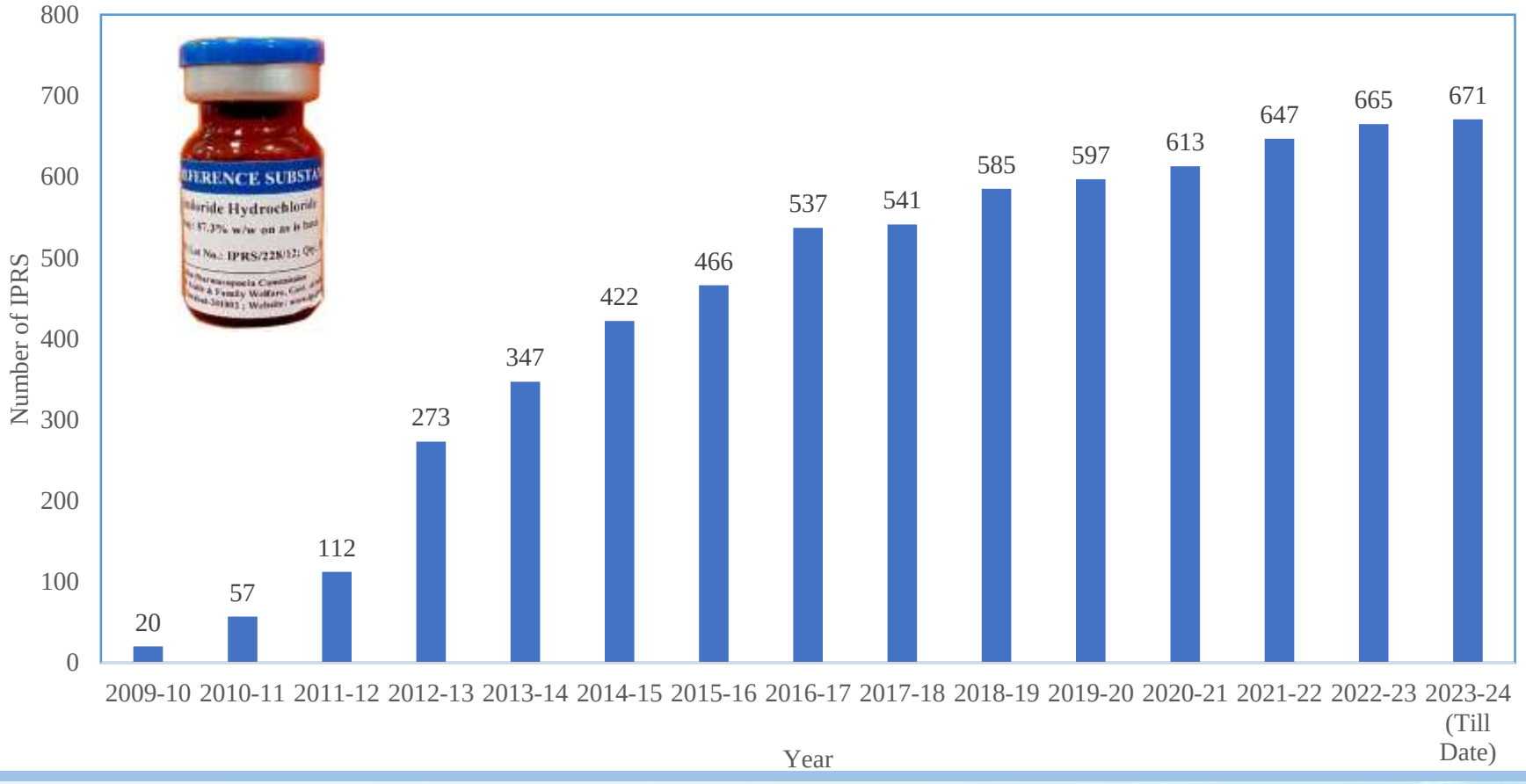
Types of IPRS at IPC

Abbreviation	Full form	Representative vial image
IPRS	Indian Pharmacopoeia Reference Substances	
IMP-RS	Impurity Reference Substances	
IPPRS	Indian Pharmacopoeia Phytochemical Reference Substances	
IPBRS	Indian Pharmacopoeia Botanical Reference Substances	

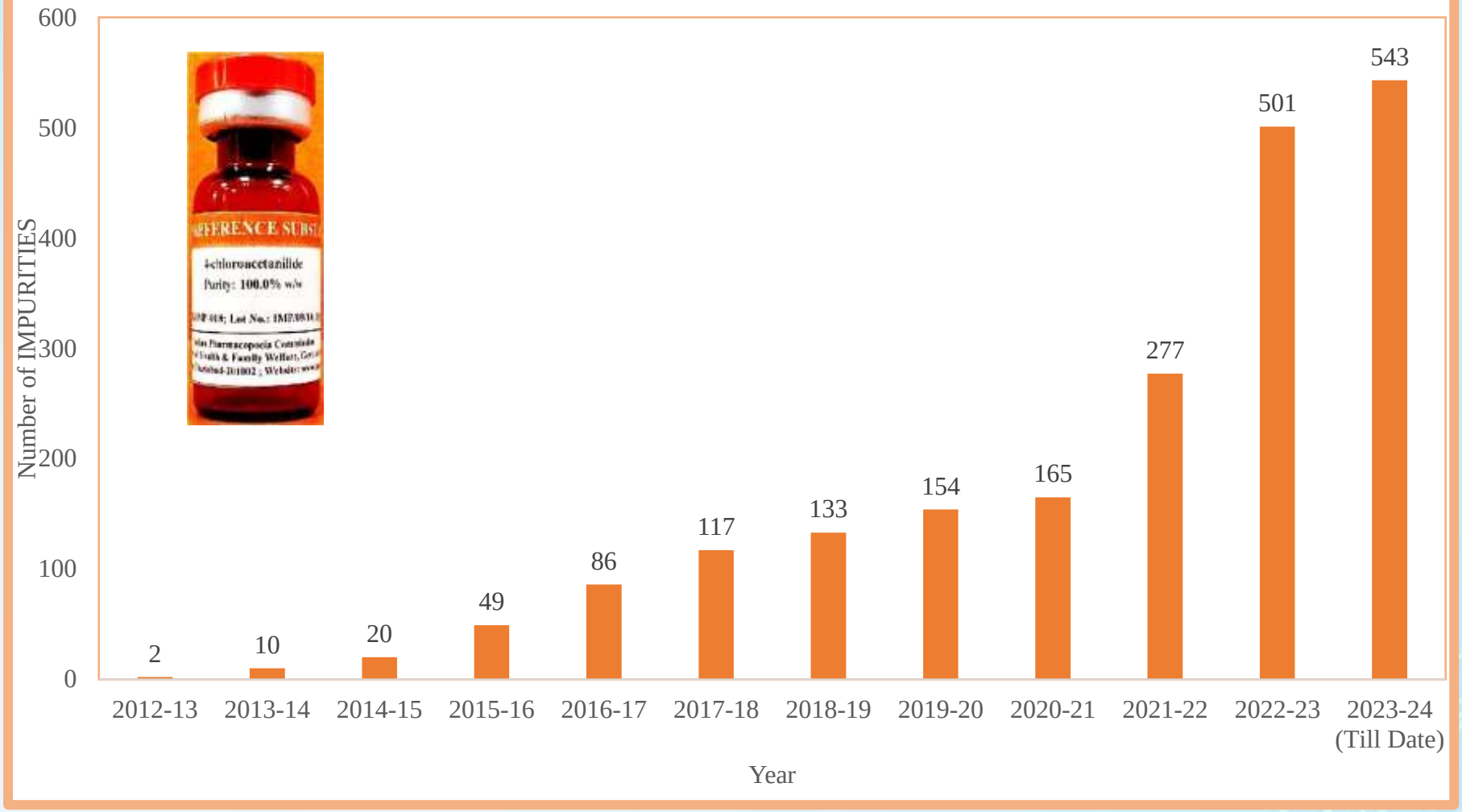
Availability of IPRS and Impurity RS

Particulars/ Item	No. of available standards available at IPC Ghaziabad
IPRS	671
Impurity RS	543

Development of IPRS



Development of Impurity RS



COA: IPRS

IPC/CHEM/STP/002/09/FMT/05

INDIAN PHARMACOPOEIA COMMISSION

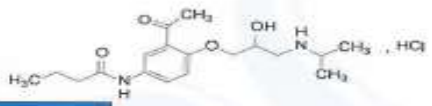
(MINISTRY OF HEALTH AND FAMILY WELFARE, GOVT. OF INDIA)
SECTOR-23, RAJ NAGAR, GHAZIABAD-201002
Tel No: 0120-2783392, 2783400, 2783401; Fax: 2783311
Mail: lab.ipc@gmc.in, Web: www.ipc.gov.in

CERTIFICATE OF ANALYSIS

Acebutolol Hydrochloride

(*RS*)-3'-acetyl-4'-(2-hydroxy-3-isopropylaminopropoxy)butyranilide hydrochloride

Structure:



IDENTIFICATION

Lot No.: IPRS/33/20	**Catalogue Number**: A-023
Unit Quantity: 200 mg	**Chemical Formula**: $C_{18}H_{28}N_2O_4.HCl$
Molecular Weight: 372.9	**Assigned Value (Purity)**: 0.996 mg per mg on as is basis
Validity Date*	
Storage: Store between 2°C to 8°C, protected from light and moisture	

Intended Use

IPRS/CRM is intended for use in pharmaceutical testing, R&D, Validation or Quality Control of Analytical Methods with specified quantity. This Material cannot be used as "Drug" or household.

Instruction for handling and use

Allow the sealed container to equilibrate at ambient/room temperature before opening for use. Do not dry, use "As on basis". Once the container has been opened, Stability of content, value cannot be guaranteed. It is for immediate use.

Safety Information

Refer to the material safety data sheet

(Dr. Anuj Prakash)
Principal Scientific Officer
Approving Officer

Indian Pharmacopoeia Commission is NABL ISO/IEC 17025:2017, ISO/IEC 17043:2010, ISO/IEC 17034:2016and Accredited and WHO pre-qualified Laboratory

COA are now available online on IPC website i.e. ipc.gov.in Individual can download the particular COA of IPRS/Impurity after entering CAT no. written on purchased vial.

Purity is "on as is basis"

COA: IMPRS

IPC/CHEM/STP/002/09/FMT/05

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(MINISTRY OF HEALTH AND FAMILY WELFARE, GOVT. OF INDIA)
SECTOR 23, RAJ NAGAR, GHAZIABAD-201002
Tel No: 0120-2783392, 2783400, 2783401, Fax: 2783311
Mail: lab.ipc@gov.in, Web: www.ipc.gov.in

CERTIFICATE OF ANALYSIS

Clotrimazole Imp E

2-chlorobenzophenone

Structure:

IDENTIFICATION

Lot No.: IMP/04/16	**Catalogue Number**: IPRS/IMP-065
Unit Quantity: 20 mg	**Chemical Formula**: $ClC_6H_4COC_6H_5$
Molecular Weight: 216.66	**Purity**: 98.8 % w/w
Validity Date*	
Storage: Store between 2°C to 8°C, protected from light and moisture	

Intended Use

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Indian Pharmacopoeia Commission is NABL **ISO/IEC 17025:2017, ISO/IEC 17043:2010, ISO/IEC 17034:2016** and Accredited and **WHO pre-qualified** Laboratory

How to Purchase IP Reference Substances

Offline Mode

Go to ipc.gov.in site home page
Click on Offline under the Order IPRS Eservices menu

A new page containing Supply order form will appears

Download and fill the form

Make payment as per your items through NEFT/DD mentioned the payment details in the form

Send the hard/Soft copy to IPC address or through email

Order placed

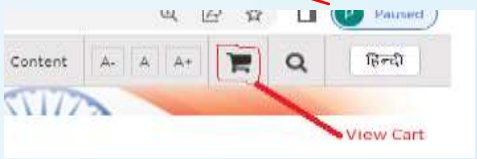
Online Mode

Go to ipc.gov.in site home page
Click on Online Services

Click on product (IPRS/IMP-RS/IPPRS/IPBRS etc) wish to purchase

A new page appear containing the list of products

Click on add to cart for purchase (Multiple Item can be added to the cart) Click on cart available on the right top (as shown in image)



Checkout-fill login details/Delivery detail/ Payment method and confirm order

DEG/EG/PG; brief introduction

- Diethylene glycol (DEG) and Ethylene glycol (EG) are used for antifreeze, in cooling and heating systems etc.
- DEG/EG have similar physical properties to Glycerin and Propylene Glycol (PG), including natural sweetness. This facilitates the adulteration of Glycerin and PG with less expensive, more toxic DEG/EG.
- DEG/EG are both metabolized by alcohol and aldehyde dehydrogenases to produce toxic metabolites.
- Both glycols produce coma, seizures, metabolic acidosis and renal failure, through by different mechanisms.
- In several medication associated DEG mass poisonings, the clinical picture included ARF and neurologic symptoms, including encephalopathy, coma, and death.

Monographs in IP containing DEG/EG Impurities

- Propylene Glycol
- Glycerin
- Sorbitol solution (70%) crystalline
- Sorbitol Solution (70%) non-crystalline

} Amendment list 04

Sample/ standard preparation

Preparation of vial for blank: Diluent as such in GC vial

Preparation of Internal Standard: 0.01% w/v of *2,2,2-Trichloroethanol* in methanol.

Preparation of Standard Stock solution:

A) Propylene Glycol Stock Solution: Weight accurately 125 mg of Propylene Glycol in 100 ml volumetric flask, dissolve & dilute to 100 ml with methanol (1.25mg/ml or 1250 ppm)

B) Ethylene Glycol Stock Solution: Weight accurately 125 mg of Ethylene Glycol in100 ml volumetric flask, dissolve & dilute to 100 ml with methanol (1.25mg/ml or 1250 ppm)

C) Diethylene Glycol Stock Solution: Weight accurately 125 mg of Diethylene Glycol in100 ml volumetric flask, dissolve & dilute to 100 ml with methanol (1.25mg/ml or 1250 ppm)

D) 2.2,2-Trichloroethanol Stock Solution: Weight accurately 250 mg of 2,2,2- Tri chloroethanol (Internal Standard) in 100 ml volumetric flask, dissolve & dilute to 100 ml with methanol (2.50mg/ml)

Sample/ standard preparation

- **System Suitability solution:** Transfer 1 ml from each solution A, B, C & D to 25 ml volumetric flask, dissolve & dilute to 25 ml with methanol (50 ppm).

- **Standard Solution:** Use System suitability solution as standard solution.

- **Test solution:** Transfer 5 gm from syrup and 1.0 ml from standard stock solution D in to 25 ml volumetric flask, dissolve & dilute to 25 ml with methanol (20 %w/v). Shake vigorously for 5 to 10 minutes, allow to stand for 5-10 minutes and filter the supernatant liquid or centrifuge for 2-3 minutes and filter the upper layer. Transfer in GC vials

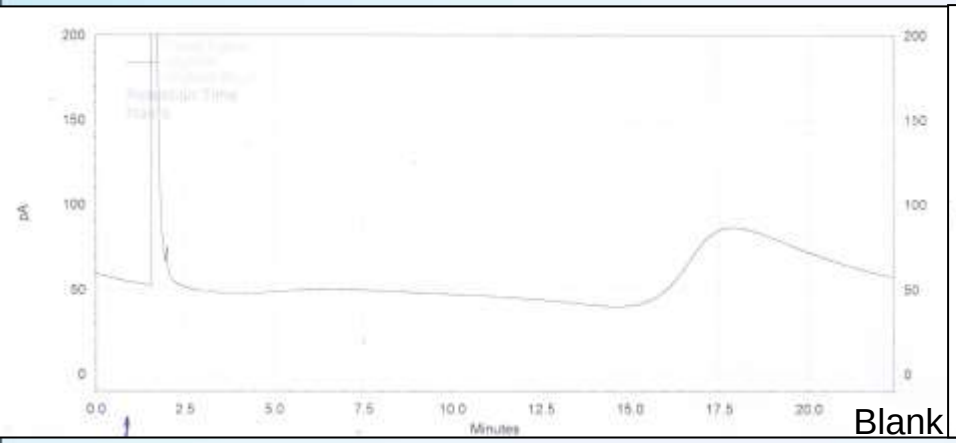
- **Test Recovery solution:** Transfer 5 gm from syrup and 1.0 ml from each solution A, B, C & D to 25 ml volumetric flask, dissolve & dilute to 25 ml with methanol (20%w/v test sample + 50 ppm each of EG, PEG, DG) Shake vigorously for 5 to 10 minutes, allow to stand for 5-10 minutes and filter the supernatant liquid or centrifuge for 2-3 minutes and filter the upper layer. Transfer in GC vials.

SST Criteria

- ✓ The **resolution** between ***ethylene glycol and propylene glycol*** peaks should not be less than 3.0
- ✓ The **relative standard deviation** of peak ratio areas obtained for each content from six injections of standard preparation should not be more than 8.0%.
- ✓ The relative standard deviation of peak ratio areas obtained for each content from six injections of standard preparation and bracketing standard should not be more than 8.0%.
- ✓ The acceptance criteria of Recovery is 80% - 120%

Note: Bracketing standard should be injected at the end of sequence or after injecting ten injections of test preparations, whichever is earlier.

Chromatograms



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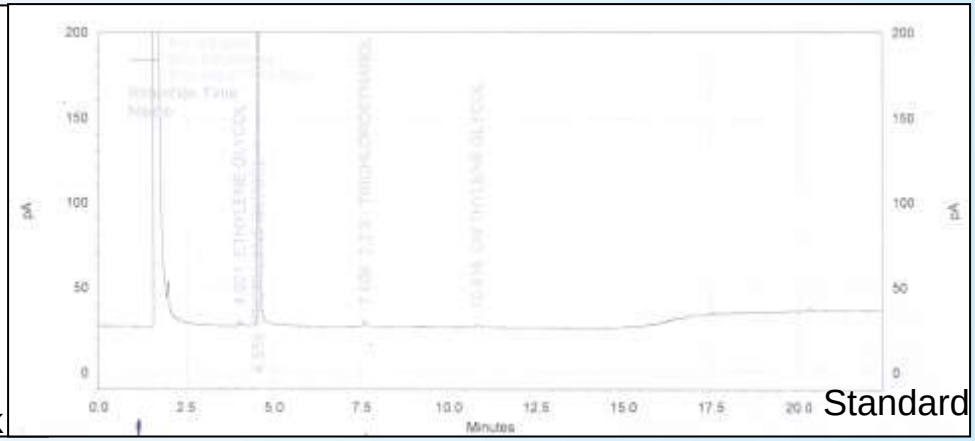
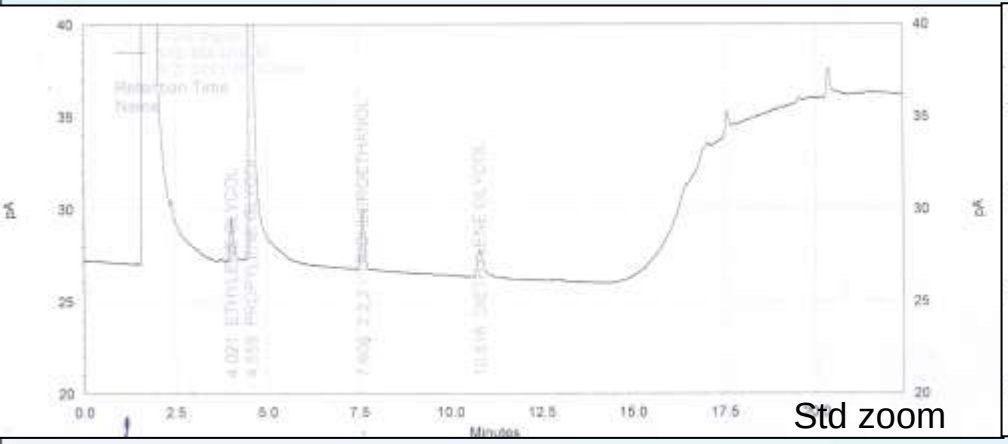
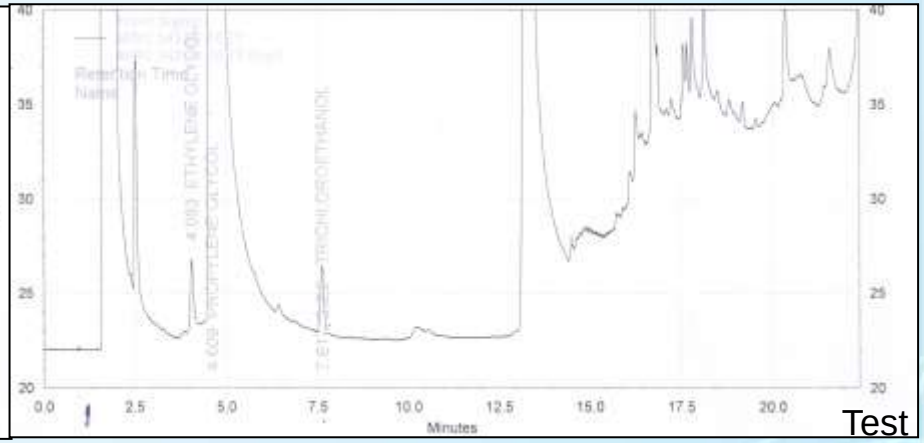


Standard



Std zoom



Test

Acceptance Criteria

Component	Limits NMT (%)
Ethylene glycol	0.10
Diethylene glycol	0.10

Notification issued by DCG(I)

File No: DCGI/MISC/2023/09
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
FDA Bhawan, Kotla Road, New Delhi-110002

Date: 25th, May, 2023

To,
All State Drug Controllers/UTs
All CDSCO Zonal, Sub-Zonal, Port offices,
All Indian Drug manufacturers Associations

Subject: - Procedure for submission of cough syrups to be exported by the manufacturer/authorised person of manufacturer/exporter directly to any of the Central/NABL State accredited laboratories for testing purpose-reg.

Ref:- 1. Notification no. 06/2023 dated 22nd May, 2023
2. D.O. Letter No.X-11035/40/2023-DRS dated 23.05.2023

Sir,

Ministry of Commerce & Industry, Government of India vide Notification no. 06/2023 dated 22nd May, 2023 shall be permitting export of cough syrups, subject to the export sample being tested and production of Certificate of Analysis (CoA) issued by any of the Central Government Laboratories and any NABL accredited State Drug Testing Laboratory. Accordingly, Joint Secretary (R) MoH&FW, Government of India issued D.O. letter No. X.11035/04/2023-DRS on dated 23rd May, 2023 to all State Drug Controllers to actively engage with the manufacturer/export houses and relevant associations to ensure that this process goes smoothly.

In order to facilitate the process of testing of cough syrups at the said laboratories the following are the pre-requisite/requirements for submission of samples by the manufacturer directly to the nearby NABL accredited State / Central laboratories as mentioned in the notification issued by the Department of Commerce (**Ref.1**):

1. Covering letter from the manufacturer/exporter on letter head addressed to concerned laboratory.
2. Manufacturing license of the product for export purpose.
3. Export order
4. Representative sample from the export consignment.
5. Thrice the quantity required for performing complete analysis of the sample.
6. Qualitative composition of product including excipients.
7. Certificate of analysis by the manufacturer of the particular batch and method of analysis (STP).
8. Reference/working standard (with traceability certificate) and Placebo as applicable.

File No: DCGI/MISC/2023/09
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
FDA Bhawan, Kotla Road, New Delhi-110002

Date: 26th May, 2023

To,
All State Drug Controllers/UTs
All CDSCO Zonal, Sub-Zonal, Port offices,
All Drug manufacturers Associations

Subject: - Clarifications with respect to submission of samples of cough syrups to be exported by the manufacturer/authorised person of manufacturer/exporter directly to any of the Central/NABL accredited State laboratories for testing purpose-reg.

Ref:- 1. Notification no: 06/2023 dated 22nd May 2023, Ministry of Commerce & Industry, Govt. of India.
2. D.O. Letter No. X-11035/40/2023-DRS dated 23.05.2023 JS (R), MoHFW, Govt. of India
3. Directorate Lr. No. DCGI/MISC/2023/09 dated 25.05.2023.

Sir,

Further to this Directorates Letter vide File No. DCGI/MISC/2023/09 dated 25.05.2023 and the representations received, this is to clarify that

1. Cough Syrups are liquid formulations for oral use which contains cough suppressants, expectorants, antihistamines, sympathomimetics, bronchodilators or mucolytic agents either alone or in combinations and are used for treatment of cough and cold that fall under Allopathic System of Medicine and are meant for export, shall be tested by IPC, CDSCO Laboratories and NABL accredited State Drugs Testing Laboratories as specified in the Ministry of Commerce & Industry Notification no: 06/2023 dated 22nd May 2023 and D.O. Letter No. X-11035/40/2023-DRS dated 23.05.2023 JS (R), MoHFW, Govt. of India.

In view of above, all State Licensing Authorities/CDSCO Zonal, Sub-Zonal Offices and all Indian Drug Manufacturer Association are requested to percolate the above requirements to all concerned who intend to export cough syrups.

Yours faithfully,

(Dr. Rajeev Singh Raghuvanshi)
Drugs Controller General (India) &
Central Licensing Authority

Copy to:

1. The Drugs Controller for the State of Gujarat/Karnataka/Kerala/Madhya Pradesh/Maharashtra/Jammu & Kashmir and Uttarakhand.
2. All Directors of NABL accredited State Laboratories of Gujarat/Karnataka/Kerala/Madhya Pradesh/Maharashtra/Jammu & Kashmir and Uttarakhand.
3. Secretary-cum-Scientific Director, IPC, Ghaziabad.
4. Head of laboratories of CDL, Kolkata.
5. Head of laboratories of CDTL, Chennai, Mumbai and Hyderabad.
6. Head of laboratories of RDTL, Guwahati, Chandigarh.

With a request to test DEG/EG in all samples even if it is not part of the mft. specifications along with other test parameters and issue the test report as per the format enclosed.

Way Forward

- Drug product manufacturers should know their supply chain for glycerin (i.e., the manufacturer of the component and any subsequent distributor(s)).

- All manufacturers take every opportunity to ensure proper testing of glycerin for DEG contamination. All personnel in pharmaceutical manufacturing facilities (especially personnel directly responsible for receipt, testing, and release of glycerin) should be made aware of the importance of proper testing and the potential hazards if the testing is not done.

- Repackers, and others who distribute and prepare glycerin for use in drug products, test glycerin that is used, sold for use, or intended for use in drug products.

- For other components, such as PG, that in the past were found to be contaminated with DEG, precautions should also be taken to identify reliable suppliers and secure shipment to prevent similar occurrences.

Accreditation/ Certification at IPC

NABL Accreditation

- Indian Pharmacopoeia Laboratory is accredited for Chemical and Biological Testing as per ISO 17025:2017 by National Accreditation Board for Testing & Calibration Laboratory (NABL) from 2011 onwards.

Reference Material Producer (RMP)

- IPC (Reference Standard Division) has been certified as Reference Material Producer as per ISO 17034:2016 from 2016 onwards.

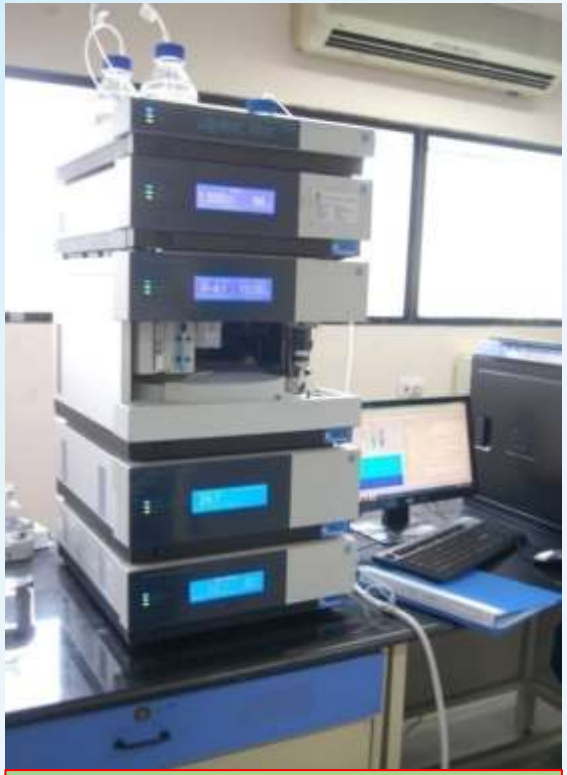
Proficiency Testing Provider (PT)

- IPC has been certified as Proficiency Testing Provider as per ISO 17043:2010 from 2017 onwards.

WHO prequalified Laboratory

- IPC has been certified as prequalified QCL (Quality Control Laboratory) by WHO since 2015.

Instruments in IPC Laboratory



UHPLC: Ultimate High Performance Liquid Chromatography

IPC Laboratory

FT-IR: Fourier Transform Infrared Spectroscopy

Instruments in IPC Laboratory

NMR- Nuclear Magnetic Resonance Spectroscopy

LC-MS-MS: Liquid Chromatography Mass Spectrometry(Q-TOF)

Instruments in IPC Laboratory

GC-HS-Gas Chromatography Head Space

CHNS-Carbon Hydrogen Nitrogen Sulfur Analyzer

Instruments in IPC Laboratory

ICP-MS-Ion Coupled Plasma Spectroscopy

DSC-Differential Scanning Colorimeter

Thank You

USE OF IP & IPRS IS SOCIAL AND LEGAL OBLIGATION FOR "IP" PRODUCTS