The International Pharmacopoeia - Overview

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Quality Assurance and Safety: Medicines

World Health Organization

The International Pharmacopoeia – Ph. Int.

- ***Scope***
- ***WHO Consultative procedure***
- ***What's new***
- ***Link with other programmes and organisations***

Pharmacopoeias

Pharmacopoeias may be:

- National — e.g. Brazilian, British, Chinese, Indian, Japanese, Mexican, Spanish, United States
- Regional — e.g. European
- International — *The International Pharmacopoeia*

Pharmacopoeias

National and regional pharmacopoeias

- Cover medicines used in the relevant country or region
- Are legally binding "official" in the relevant country or region
- Are prepared by a national or regional authority

International Pharmacopoeia
A few dates…

The history of the *International Pharmacopoeia* dates back 1874…

→ **1948** First ***World Health Assembly*** established Expert Committee on Unification of Pharmacopoeia

→ **1950** WHA approved publication of *Pharmacopoeia Internationalis*

International Pharmacopoeia

A collection of monographs and requirements for:

- → **Drug substances**
- → **Excipients**
- → **Finished dosage forms**
- → **General methods and requirements:**
  - → dosage forms, *e.g. tablets, liquid preparation for oral use*
  - → *dissolution testing*
- → **Supplementary information,** *e.g. General guidelines for Chemical Reference Substances*
- → **Infrared reference spectra**

International Pharmacopoeia

Scope since 1975

→ **Model Lists of Essential Medicines and**

→ **Medicines recommended and specifications needed by WHO Programmes, e.g. to treat Malaria, TB, HIV/AIDS and for children!**

International Pharmacopoeia

Special features

….when ***complex, technically demanding methods*** are described (e.g. HPLC),

--> a less technically demanding ***analytical method*** (e.g. TLC) proposed as **alternative** (if possible).

International Pharmacopoeia

→ *implementation:* **“ready for use” by Member States**

"The Ph.Int […] is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. The pharmacopoeia, or any part of it, shall have legal status, whenever a national or regional authority expressly introduces it into appropriate legislation."

*[Reference to **World Health Assembly resolution WHA3.10**,*
WHO Handbook of Resolutions and Decisions, Vol. 1, 1977, p. 127]

How does the Ph. Int. function?

- The Ph. Int. is guided by the **Expert Committee on Specifications for Pharmaceutical Preparations**
- Aim over the last 60 years:

  "to promote quality assurance and quality control of pharmaceuticals"

- Meets once a year for a week in WHO HQ, Geneva

WHO Consultative procedure

- The process is designed to ensure **wide consultation** and **transparency** during monograph development and to make the adopted texts available in a timely manner.

WHO Procedure for the preparation of drug Quality Control specifications (1) …..or why it takes so long….

- **Step 1**: **Identification of specific pharmaceutical products** for which Quality Control (QC) specifications need to be developed, **confirmation by all WHO parties** concerned (including Department of Essential Medicines and Pharmaceutical Policies (EMP) specific disease programmes and the Prequalification Programme)
- **Step 2***: Provision of **contact details from manufacturers** of the above products in collaboration with all parties concerned
- **Step 3***: Contact manufacturers for provision of **QC specifications and samples**
- **Step 4**: **Identify** and **contact QC laboratories** for **collaboration** in the project (2-3 laboratories depending on how many pharmaceutical products have been identified in step 1), Contract for laboratory work

WHO Procedure for the preparation of drug Quality Control specifications (2) …..or why it takes so long….

- **Step 5**: Prepare the **contract** for drafting the specifications and undertaking the necessary laboratory work
- **Step 6:** Search for **information on QC specifications** available in the **public domain**
- **Step 7**: **Laboratory testing**, **development** and **validation** of **QC Specifications**
- **Step 8**: Support WHO Collaborating Centre in the **establishment of International Chemical Reference Substances**
- **Step 9**: Follow the **consultative process**, mailing of draft specifications to Expert Panel and specialists

WHO Procedure for the preparation of drug Quality Control specifications (3) …..or why it takes so long….

- **Step 10**: **Discussion of comments** with contract laboratories, WHO Collaborating Centres, additional laboratory testing to **verify and/or validate specifications**
- **Step 11**: Consultation to **discuss the comments and test results received** as feedback
- **Step 12**: recirculation **for comments**
- **Step 13**: as step 10
- **Step 14**: **Present the drafts** to the WHO Expert Committee on Specifications for Pharmaceutical Preparations for possible **formal adoption**,

… if not adopted repetition of steps 11 to 13 as often as necessary

WHO Procedure for the preparation of drug Quality Control specifications (4) …..or why it takes so long….

… If adopted proceed to step 15.

- **Step 15: Incorporate all changes agreed** during the discussion leading to adoption together with any editorial points. Where necessary, also take account of any further comments that may still be received due to comment deadlines for recirculated texts (Step 12 and beyond) falling shortly after the meeting.

- **Step 16:** In all cases, **confirm the amended text** by correspondence with the relevant experts and/or contract laboratory before making it available on the WHO Medicines website.

- **Step 17: Make "final texts" available on the Medicines website** to provide users such as PQ assessors and manufacturers with the approved specifications in advance of the next publication date.

Requirements for samples

200 units:	tablets, capsules
300 ml for:	oral solution/suspension, injection
2 x 40 g for:	API
5 g for:	unpurified API
5 g for:	intermediates
some mg for:	individual impurities

Requirements for specifications (1)

Manufacturer's documentation is kept confidential

- **Description, Chemistry, Solubility, Storage, Labelling**
- **Definition,** with information on **polymorphism** if relevant
- **Identification**
- **Assay**
- **Specific tests** (sulphated ash, optical rotation, loss on drying…)
- **Related substances**

Requirements for specifications (2)

- **Precise description of analytical methods**
- **Impurities (chemical names, structures, origin)**

Any relevant information on

- **Performance testing** (e.g. dissolution)
- **Stability**
- **Validation of analytical methods**

World Health Organization

International Pharmacopoeia

→ *current:* **4th Edition + 1st Supplement**

→ Consolidated in :

2 Volumes - *Vol. 1:* *pharmaceutical substances* (A-O)

- *Vol. 2:* *pharmaceutical substances (P-X)*
+ dosage forms + radiopharmaceuticals
+ methods of analysis + reagents

1st Supplement - *new requirements and revisions*

Available in ***Publication***, ***CD-ROM*** *and* ***Online***

http://www.who.int/medicines/publications/pharmacopoeia/overview/

4th Edition – new (1)

4th Edition

- →*Monographs on **antiretrovirals** (ARVs)*
- →***Revision** of existing monographs*
- →*Improved **presentation***
- →*Improved **cross-referencing** to **general methods***
- →*Improved **search functions** for CD-ROM and online version*
- →*New notice on **"manufacture"***
- →*New notice on **impurities***
- →*New **list of impurities** shown to be controlled by tests*

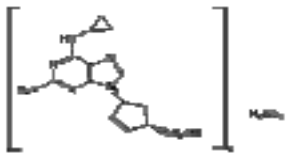
4th Edition – new (2)

First Supplement

→*About **30 New monographs** for medicines for **HIV/AIDS**, **TB** and **Malaria**, including some **for children***

→*Revisions, **125 IR reference spectra**, supplementary info*

ABACAVIRI SULFAS
ABACAVIR SULFATE



$(C_{14}H_{18}N_6O)_2,H_2SO_4$

Relative molecular mass. 670.8

Chemical name. Abacavir sulfate is (1*S*,4*R*)-4-[2-Amino-6(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol hemisulfate; CAS Reg. No. 188062-50-2.

Description. White to almost white powder.

Solubility. Freely soluble in water.

Category. Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).

Storage. Abacavir sulfate should be kept in a well-closed container.

Requirements

Definition. Abacavir sulfate contains not less than 99.0 % and not more than 101.0 % of $(C_{14}H_{18}N_6O)_2,H_2SO_4$ calculated with reference to the anhydrous substance.

Manufacture. The production method is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 0.5% for (1*R*, 4*S*)-abacavir enantiomer using a suitable chiral chromatographic method.

Identity tests

• Either tests A, B, D and E or tests C, D and E may be applied

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 8 volumes of dichloromethane R and 2 volumes of 2-propanol R as the mobile phase. Apply separately to the plate 5 µl of each of 2 solutions in methanol containing (A) 5 mg of the test substance per ml and (B) 5 mg of abacavir sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120°C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B. The absorption spectrum (1.6) of a 15 µg per ml solution, when observed between 210 and 300 nm, exhibits a maximum at about 291nm; the specific absorbance ($A_{1cm}^{1\%}$) is between 399 and 441 nm.

C. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from abacavir sulfate RS or with the *reference spectrum* of abacavir sulfate.

D. Determine the specific optical rotation (1.4) using a 10 mg/ml solution and calculate with reference to the anhydrous substance; $[\alpha]_D^{20°C}$ between −52 ° and −57°.

E. A 10 mg/ml solution yields reaction A described under 2.1 General identification tests, as characteristic of sulfates.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 1; determine the heavy metal content according to Method A; not more than 20 µg/g.

Sulfated ash (2.3). Not more than 2.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A. Use 1.0 g of the test substance. The water content is not more than 5 mg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm), packed with octadecylsilyl silica gel for chromatography (5 µm).

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 0.05 % solution of trifluoroacetic acid R.
Mobile phase B: 85 volumes of methanol R and 15 volumes of water.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 - 20	95 to 70	5 to 30	Linear gradient
20 - 35	70 to 10	30 to 90	Linear gradient
35 - 40	10 to 95	90 to 5	Return to initial composition
40 - 45	95	5	Re-equilibration

Chemical name in accordance with IUPAC nomenclature rules

CAS number

Alternative tests

Reagents

International chemical reference substance (ICRS)

Cross-reference to a general method

Operate with a flow rate of 0.8 ml per minute and the column oven temperature at 30 °C. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Prepare the following solutions in the dissolution solvent prepared by diluting 1 ml of phosphoric acid (~1440g/l) TS in 1 litre of water.

For solution (1) dissolve 10 mg of the test substance in the dissolution solvent and dilute to 50.0 ml with the same solvent. For solution (2) dilute 5.0 ml of solution (1) to 50.0 ml with the dissolution solvent. Then dilute 5.0 ml of this solution to 50.0 ml with the same solvent. For solution (3) dissolve 5 mg of abacavir sulfate for system suitability RS (containing abacavir sulfate and impurities B to F) in the dissolution solvent and dilute to 25 ml with the same solvent.

Inject separately 20µl each of solutions (1), (2) and (3) and of the dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the impurity peaks are eluted at the following relative retention with reference to abacavir (retention time about 19 minutes): impurity C about 0.6; impurity D about 1.05; impurity E about 1.10; impurity B about 1.3; impurity F about 1.7. The test is not valid unless the resolution between the peaks corresponding to abacavir and impurity D is at least 1.5.

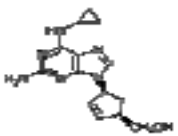
In the chromatogram obtained with solution (1) the area of any individual peak corresponding to impurity C, D, E, B, or F is not greater than 0.3 times the area of the principal peak obtained with solution (2) (0.3%). The area of any other impurity peak is not greater than 0.1 times the area of the principal peak obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than the area of the principal peak obtained with solution (2) (1%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%).

Assay. Dissolve about 0.300 g, accurately weighed, in 50 ml of water and titrate with sodium hydroxide (0.1 mol/l) VS, determining the end-point potentiometrically.

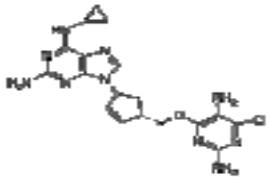
Each ml of sodium hydroxide (0.1 mol/l) is equivalent to 33.54 mg of $(C_{14}H_{18}N_6O)_2,H_2SO_4$.

Impurities

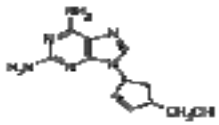
List of known and potential impurities that have been shown to be controlled by this monograph



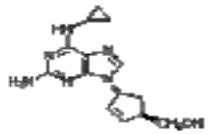
A. (1*R*, 4*S*)-abacavir sulfate enantiomer [see under Manufacture],



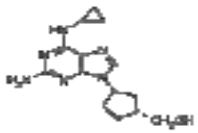
B. *N*^{6}-cyclopropyl-9-((1*R*,4*S*)-4-{[(2,5-diamino-6-chloro-4-pyrimidinyl)oxy]methyl}-2-cyclopenten-1-yl)-9*H*-purine-2,6-diamine,



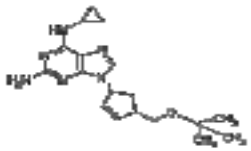
C. [(1*S*,4*R*)-4-(2,6-diamino-9*H*-purin-9-yl)-2-cyclopenten-1-yl]methanol,



D. {(1*R*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopenten-1-yl}methanol,



E. {(1*R*,4*S*)-3-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl] cyclopentyl}methanol,



F. *N*^{6}-cyclopropyl-9-((1*R*,4*S*)-4-{[(1,1-dimethylethyl)oxy]methyl}-2-cyclopenten-1-yl)-9*H*-purine-2,6-diamine.

ABACAVIRI COMPRESSI
ABACAVIR TABLETS

Category. Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).

Storage. Abacavir tablets should be kept in a well-closed container.

Labelling. The designation of the container of Abacavir tablets should state that the active ingredient is in the sulfate form and the quantity should be indicated in terms of the equivalent amount of abacavir.

Cross-reference to the EMLs

Additional information. Strength in the current WHO Model list of essential medicines: 300 mg of abacavir. Strength in the current WHO Model list of essential medicines for children: 300 mg of abacavir.

Requirements

Comply with the monograph for "Tablets".

Cross-reference to the general monograph

Definition. Abacavir tablets contain Abacavir sulfate. They contain not less than 90.0% and not more than 110.0% of the amount of abacavir ($C_{14}H_{18}N_6O$) stated on the label.

Identity tests

- Either tests A, C and D, or tests B, C and D may be applied.

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica R6 as the coating substance and a mixture of 8 volumes of dichloromethane R, 2 volumes of 2-propanol R as the mobile phase. Apply separately to the plate

5 µl of each of the following 2 solutions in methanol R. For solution (A) shake a quantity of the tablets containing the equivalent of 25 mg of abacavir with 5 ml, filter, and use the clear filtrate. For solution (B) use 6 mg of abacavir sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120°C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B. See method A described under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

C. To a quantity of powdered tablets containing the equivalent of 15 mg abacavir add 100 ml of water R, shake and filter. Dilute 5 ml of the filtrate to 50 ml with the same solvent. The absorption spectrum (1.6) of the resulting solution, when observed between 220 nm and 320 nm, exhibits a maximum at about 291 nm.

D. To a quantity of the powdered tablets containing the equivalent of about 20 mg of abacavir add 5 ml of water R and shake. The resulting solution yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the chromatographic conditions as described under Assay method A.

Prepare the following solutions in the dissolution solvent prepared by diluting 1 ml of phosphoric acid (~ 1440 g/l) TS in 1 litre of water R.

For solution (1) transfer a quantity of the powdered tablets containing the equivalent of 10 mg of abacavir in the dissolution solvent and dilute to 50.0 ml with the same solvent. For solution (2) dilute 5.0 ml of solution (1) to 50.0 ml with the dissolution solvent. Then dilute 5.0 ml of this solution to 50.0 ml with the same solvent. For solution (3) dissolve 5 mg of abacavir sulfate for system suitability RS (containing abacavir sulfate and impurities B to F) in the dissolution solvent and dilute to 25 ml with the same solvent.

Inject separately 20 µl each of solution (1), (2) and (3) and of dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the impurity peaks are eluted at the following relative retention with reference to abacavir (retention time about 19 minutes): impurity C about 0.7; impurity D about 1.05; impurity E about 1.10; impurity B about 1.3; impurity F about 1.7. The test is not valid unless the resolution between the peaks due to abacavir and impurity D is at least 1.5.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity C is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%); the area of any peak with a relative retention less than that of impurity C (impurity G) is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%); the area of any other peak, apart from the principal peak, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%). The sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay

Alternative methods for assay

• Either method A or method B my be applied

A. Weigh and powder 20 tablets. Carry out the test under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm), packed with octadecylsilyl silica gel for chromatography (5 µm).

The mobile phases for gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 0.05% solution of trifluoroacetic acid R in water R.

Mobile phase B: 85 volumes of methanol R and 15 volumes of water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 - 20	95 - 70	5 to 30	Linear gradient
20 - 35	70 - 10	30 to 90	Linear gradient
35 - 40	10 - 95	90 to 5	Return to initial composition
40 - 45	95	5	Re-equilibration

Operate with a flow rate of 0.8 ml per minute and the column oven temperature at 30 °C. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm. Prepare the following solutions in the dissolution solvent prepared by diluting 1 ml of phosphoric acid (~ 1440 g/l) TS in 1 litre of water R.

For solution (1) transfer a quantity of the powdered tablets containing the equivalent of about 20 mg of abacavir, accurately weighed, to a 100-ml volumetric flask. Add about 80 ml of dissolution solvent, sonicate for about 5 minutes, allow to cool at room temperature, and make up to volume using the same solvent. Filter a portion of this solution through a 0.45-µm filter, discarding the first few ml of the filtrate. For solution (2) use 0.23 mg of abacavir sulfate RS per ml of dissolution solvent.

Inject alternatively 20 µl each of solution (1) and (2) and record the chromatograms.

Measure the areas of the peak responses obtained in the chromatograms from solution (1) and (2), and calculate the content of abacavir ($C_{14}H_{18}N_6O$) in the tablets using the declared content of $(C_{14}H_{18}N_6O)_2,H_2SO_4$ in abacavir sulfate RS. Each mg of $(C_{14}H_{18}N_6O)_2,H_2SO_4$ is equivalent to 0.8537 mg of $C_{14}H_{18}N_6O$.

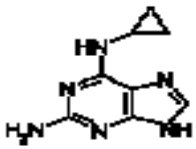
B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing the equivalent of about 15 mg of abacavir, accurately weighed, to a 100-ml volumetric flask. Add about 25 ml of water R, sonicate for about 5 minutes, allow to cool to room temperature, and make up to volume using the same solvent. Filter a portion of this solution through a 0.45-µm filter, discarding the first few ml of the filtrate. Dilute 5.0 ml of the filtrate to 50.0 ml with the same solvent. Measure the absorbance (1.6) of this solution in a 1-cm layer at the maximum at about 291 nm against a solvent cell containing water R.

Calculate the content of abacavir ($C_{14}H_{18}N_6O$) in the tablets using an absorptivity value of 42 ($A^{1\%}_{1cm}$ = 420).

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph for Abacavir sulfate and the following:

Cross-reference to impurities listed in the API monograph



G. (N^6-cyclopropyl-3*H*-purine-2,6-diamine)

Impurity specific to the dosage form

New Ph. Int. monographs - adopted by 42nd WHO Expert Committee

- **Lumefantrine**
- **Artemether and lumefantrine tablets**

- **Rifampicin, isoniazid and ethambutol tablets**
- **Rifampicin and isoniazid dispersible tablets**
- **Rifampicin, isoniazid and pyrazinamide dispersible tablets**

- **Zinc sulfate**
- **Zinc sulfate tablets, paediatric**
- **Zinc sulfate oral solution, paediatric**

- **Magnesium sulfate injection**

New Ph. Int. monographs - adopted by 43rd WHO Expert Committee

- **Efavirenz capsules**
- **Efavirenz oral solution**
- **Emtricitabine**
- **Nevirapine**
- **Nevirapine oral suspension**
- **Nevirapine tablets**
- **Zidovudine, Lamivudine and Nevirapine tablets**

New Ph. Int. monographs - adopted by 43rd WHO Expert Committee

- **Artemether and Lumefantrine oral suspension**
- **Chloroquine sulfate oral solution**
- **Quinine sulfate tablets**

- **Cycloserine**
- **Cycloserine capsules**
- **Ethambutol hydrochloride tablet**

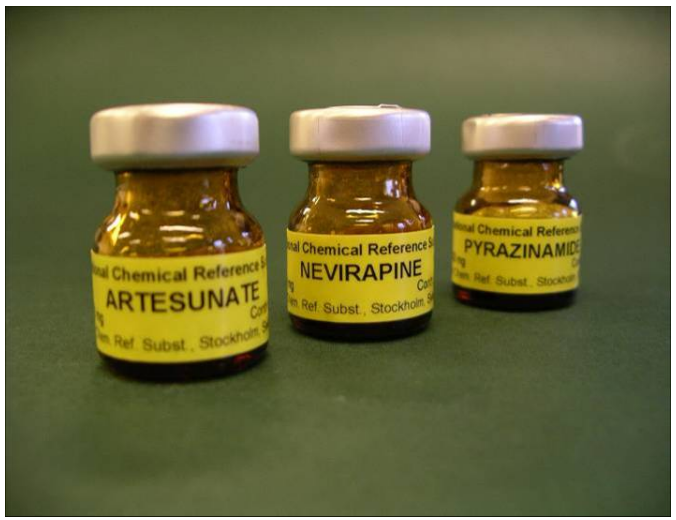
- **Mebendazole**
- **Oseltamivir phosphate**
- **Chewable Mebendazole tablets**

New Ph. Int. monographs - adopted by 43rd WHO Expert Committee

- **Fludeoxyglucose (^{18}F) injection**
- **Gallium citrate (^{67}Ga) injection**
- **Technetium (^{99m}Tc) pentetate complex injection**
- **Sodium pertechnetate (^{99m}Tc) injection (fission)**
- **Iobenguane (^{123}I) injection**
- **Sodium iodide (^{131}I) injection**
- **Sodium iodide (^{131}I) solution**
- **Sodium pertechnetate (^{99m}Tc) injection (non-fission)**
- **Thallous chloride (^{201}Tl) injection**

International Chemical Reference Substances (ICRS)

- → **207 ICRS + 12 melting point reference substances**
- → Established by **WHO COLLABORATING CENTRE FOR CHEMICAL REFERENCE SUBSTANCES**
- → **Primary reference standard**
- → **Linked to Ph.Int.**
- → Price for ICRS US$ 70
- → Includes: **- Directions for use**
  - Certificate of analysis
- → **Monitoring and on-going stability testing**
- → **Can be used for tests and analysis not included in Ph.Int.**

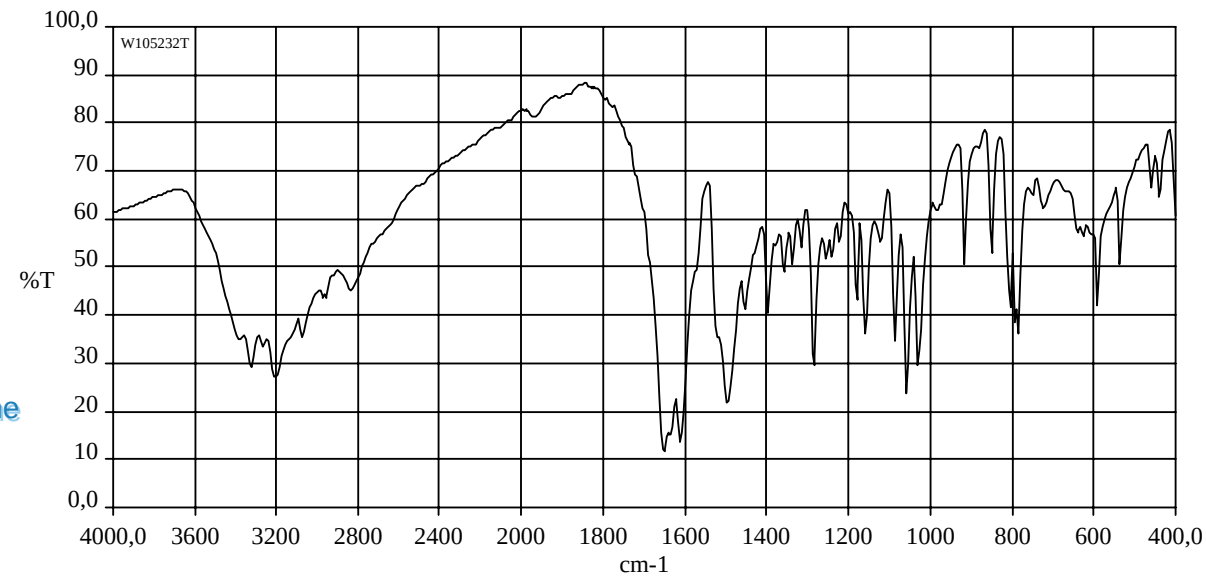


International Infrared Reference Spectra

- → Established by **WHO COLLABORATING CENTRE FOR CHEMICAL REFERENCE SUBSTANCES**
- → **155 International Infrared Reference Spectra**

  (125 published in

  ***Ph.Int. 4th Ed. Suppl. 1*)**



IR-spectrum of lamivudine

WHO's strategy for quality control

→ **Step-wise approach**:

- Basic tests (identification)
- Screening tests (TLC)
- The *International Pharmacopoeia*
- International reference materials (ICRS and IR reference spectra)

Ph.Int. and links with other programmes and organizations

- → Monographs for **ARVs**, **antimalarials**, **anti-TB drugs,** etc. (different clusters in WHO)
- → Monographs for **radiopharmaceuticals** (International Atomic Energy Agency - IAEA)
- → Monographs for **excipients** (Pharmacopoeial Discussion Group – PDG, IPEC)
- → General requirements for products derived from **plant materials** (WHO Traditional Medicines Programme)

Ph.Int. and links with other programmes and organizations

- Collaboration with **national and regional pharmacopoeias**, incl. ***Brazilian, Chinese pharmacopoeias***; ***BP, IP, JP, Ph.Eur*, *USP*,** and ***PDG***
- Collaboration with **national/regional regulatory authorities** and **quality control laboratories**
- Collaboration with **international organizations** (e.g. ***UNICEF***, ***IAEA***)
- Links with **Prequalification Programme** - A United Nations Programme managed by WHO
- Collaboration with **manufacturers** worldwide

The International Pharmacopoeia's advantages (1)

- **1. Specifications validated internationally, through an independent scientific process**
- **2. Input from WHO Collaborating Centres, national Drug Quality Control laboratories**
- **3. Collaboration with manufacturers around the world, especially for new projects**
- **4. Development considering the costs of analysis, i.e. using as few ICRS as possible**

The International Pharmacopoeia's advantages (2)

- **5. Collaboration with standard-setting organizations and parties, including regional and national pharmacopoeias**
- **6. Networking and close collaboration with WHO Member States, Drug Regulatory Authorities**
- **7. Links with other WHO activities**
- **8. FREE FOR USE by all Member States**

Quick demonstration

- The *International Pharmacopoeia* website

  http://www.who.int/medicines/publications/pharmacopoeia/en/index.html

- The WHO Medicines website

  http:www.who.int/medicines

Thank you !