Consultation documents

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The International Pharmacopoeia

Atazanavir sulfate
(Atazanaviri sulfas)

This is a draft proposal of a revised monograph for The International Pharmacopoeia (Working document QAS/17.738, March 2018). The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat: Following laboratory investigations performed to establish Atazanavir sulfate ICRS it is proposed to revise the monograph on Atazanavir sulfate with a view to:
• change the recrystallization solvent used in identity test A by IR (from methanol to acetone); and
• update the style of the monograph.
In the text available at the above-mentioned website, changes from the current monograph are indicated in the text by insert or delete.]

Molecular formula. \( \text{C}_{38}\text{H}_{52}\text{N}_6\text{O}_7\cdot \text{H}_2\text{O}_4\text{S} \)

Relative molecular mass. 802.9

Chemical names. Dimethyl (3S,8S,9S,12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[[4-(pyridin-2-yl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioate monosulfate; 2,5,6,10,13-Pentaazatetradecanedioic acid,
Atazanavir sulfate (Ph. Int.)

3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-, 1,14-dimethyl ester, (3S,8S,9S,12S)-, sulfate (1:1); CAS Reg. No. 229975-97-7.

**Description.** A white to a pale yellow powder.

**Solubility.** Freely soluble in methanol, practically insoluble in water.

**Category.** Antiretroviral (protease inhibitor).

**Storage.** Atazanavir sulfate should be kept in a tightly closed container.

**Additional information.** Atazanavir sulfate is slightly hygroscopic and may exhibit polymorphism.

**Requirements**

Atazanavir sulfate contains not less than 98.0% and not more than 102.0% of C_{38}H_{52}N_{6}O_{7}•H_{2}SO_{4}, calculated with reference to the dried substance.

**Identity tests**

- Either test A and D or test B, C and D should be applied.

**A.** 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 atazanavir sulfate RS or with the reference spectrum of atazanavir sulfate.

  If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and atazanavir sulfate RS in a small amount of acetone R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from atazanavir sulfate RS.

**B.** Carry out test B.1, or where ultraviolet (UV) detection is not available, test B.2.

**B.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 9.5 volumes of dichloromethane R and 0.5 volume of 2-propanol R as the mobile phase. Apply separately to the plate 10 μL of each of the following 2 solutions in methanol R. For solution (A) use 1 mg of the test substance per mL. For solution (B) use 1 mg of atazanavir sulfate RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or in a current of air.

  Examine the chromatogram in UV light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

**B.2** Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1, but using a plate containing silica gel R5 as the coating substance.

  Spray the plate with basic potassium permanganate (~5 g/L) TS. Examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).
C. The absorption spectrum of a 10 µg/mL solution of the test substance in methanol R, when observed between 230 nm and 340 nm, exhibits two maxima at about 250 nm and 280 nm.

D. A 20 mg/mL solution of the test substance yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

**Heavy metals.** 2.2.3 Limit test for heavy metals

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

**Loss on drying.** Dry for 3 hours at 105°C; it loses not more than 10.0 mg/g.

**Specific optical rotation.** Use a 10 mg/mL solution in equal volumes of methanol R and water R at 22°C and calculate with reference to the dried substance; the specific optical rotation is between -44° and -48°.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (150 mm × 4.6 mm) packed with end-capped, base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 µm). Use the following conditions for gradient elution:

- mobile phase A: 0.02 M phosphate buffer pH 3.5, acetonitrile R (70:30 v/v);
- mobile phase B: 0.02 M phosphate buffer pH 3.5, acetonitrile R (30:70 v/v).

Prepare the 0.02 M phosphate buffer pH 3.5 by dissolving 2.72 g of anhydrous potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 3.5 by adding phosphoric acid (~105 g/L) TS and dilute to 1000 mL with water R.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
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<td>Isocratic</td>
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<td>2–10</td>
<td>100 to 75</td>
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<td>50 to 0</td>
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<td>50–52</td>
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<tr>
<td>52–60</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
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</tbody>
</table>

Prepare the following solutions using as diluent a mixture of equal volumes of water R and acetonitrile R. For solution (1) dissolve about 50 mg of the test substance and dilute to 50.0 mL. For solution (2) dilute 10.0 mL of solution (1) to 200.0 mL. Dilute 10.0 mL of this solution to 100.0 mL. For solution (3) mix 1 mL of solution (1) with 4.5 mL of water R and 0.5 mL of sodium hydroxide (10 g/L) TS and heat the mixture in a water-bath at 85°C for 15 minutes.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C.
Inject 20 µL of solution (3). The test is not valid unless the resolution between the peak due to atazanavir (retention time about 22 minutes) and the peak with a relative retention of about 1.2 is at least 4.

Inject alternately 20 µL each of solutions (1) and (2).

In the chromatograms obtained with test solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);
- 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) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay

Dissolve 0.300 g, accurately weighed, in 30 mL of methanol R by sonication for 10 minutes. Then add 30 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) VS is equivalent to 40.145 mg of C_{38}H_{52}N_{6}O_{7}•H_2SO_4.

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Atazanavir sulfate (Ph. Int.)
Atazanavir capsules
(Atazanaviri capsulae)

This is a draft proposal of a revised monograph for The International Pharmacopoeia (Working document QAS/17.739, March 2018). The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat: Following laboratory investigations performed to establish Atazanavir sulfate ICRS it is proposed to revise the monograph on Atazanavir capsules with a view to:
• update the information given under Additional information to reflect the information given in the 20th WHO Model List of Essential Medicines; and
• use the absorptivity value of atazanavir sulfate to calculate the result of the dissolution test and assay method B.
In the text available at the above-mentioned website, changes from the current monograph are indicated in the text by insert or delete.]

Category. Antiretroviral (protease inhibitor).

Storage. Atazanavir capsules should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 100 mg, 300 mg of atazanavir (as sulfate). Strength in the current WHO EML for Children: 100 mg of atazanavir (as sulfate).

Requirements
Comply with the monograph for Capsules.

Definition
Atazanavir capsules contain atazanavir sulfate. They contain not less than 90.0% and not more than 110.0% of the amount of atazanavir, C_{38}H_{52}N_{6}O_{7}, stated on the label. Each mg of atazanavir (C_{38}H_{52}N_{6}O_{7}) is equivalent to 1.139 mg of atazanavir sulfate (C_{38}H_{52}N_{6}O_{7}\cdot H_{2}SO_{4}).

Identity tests
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 9.5 volumes of dichloromethane R and 0.5 volume of 2-propanol R as the mobile phase. Apply separately to the plate 10 µL of each of the following 2 solutions in methanol R. For solution (A) disperse a quantity of the content of the capsules containing about 20 mg of atazanavir in 10 mL of methanol R, sonicate for 10 minutes, allow to cool to room temperature, dilute to 20 mL, filter and use the filtrate. For solution (B) use 1.1 mg of atazanavir sulfate RS per mL.
Atazanavir capsules (Ph. Int.)

After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or a current of 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 a plate containing silica gel R5 as the coating substance. Spray with basic potassium permanganate (~5 g/L) TS. Examine the chromatogram in daylight.

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

B. Disperse a quantity of the content of the capsules containing about 20 mg of atazanavir in 10 mL of methanol R, sonicate for 10 minutes, allow to cool to room temperature, dilute to 20 mL and filter. Dilute 1.0 mL of the filtrate to 100.0 mL with methanol R. The absorption spectrum (1.6) of the resulting solution, when observed between 230 and 340 nm, exhibits two maxima at about 250 nm and 280 nm.

C. To a quantity of the content of the capsules equivalent to 0.2 g of atazanavir add 10 mL of a mixture of 1 volume of water R and 1 volume of acetonitrile R, shake and filter. The filtrate yields Reaction A described under 2.1 General identification tests as characteristic of sulfates.

Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium 900 mL of dissolution buffer pH 2.5 TS and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10.0 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Dilute a suitable volume of the filtrate with dissolution medium to obtain a solution containing 0.10 mg of atazanavir per mL. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 250 nm, using the dissolution medium as the blank. For each of the capsules tested, calculate the total amount of atazanavir \((C_{38}H_{52}N_6O_7)\) in the medium, using an absorptivity value of 11.4 for atazanavir sulfate \((A_{1\%}^\text{1cm} = 114)\). Each mg of atazanavir sulfate \((C_{38}H_{52}N_6O_7\cdotH_2SO_4)\) is equivalent to 1.139 mg of atazanavir \((C_{38}H_{52}N_6O_7)\).

Evaluate the results as described under 5.5 Dissolution test for solid dosage forms, Acceptance criteria. The amount in solution for each capsule is not less than 75% \((Q)\) of the amount stated on the label.

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (150 mm × 4.6 mm) packed with end-capped base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm). Use the following conditions for gradient elution:
mobile phase A: 0.02 M phosphate buffer pH 3.5, acetonitrile R (70:30 v/v);

mobile phase B: 0.02 M phosphate buffer pH 3.5, acetonitrile R (30:70 v/v).

Prepare the 0.02 M phosphate buffer pH 3.5 by dissolving 2.72 g of anhydrous potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 3.5 by adding phosphoric acid (~105 g/L) and dilute to 1000 mL with water R.

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Prepare the following solutions using as diluent a mixture of equal volumes of acetonitrile R and water R. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity of the mixed contents equivalent to 20 mg of atazanavir into a 20 mL volumetric flask. Add about 10 mL of the diluent, sonicate for 10 minutes, allow to cool to room temperature, make up to volume and filter. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) mix 1 mL of solution (1) with 4.5 mL of water R and 0.5 mL of sodium hydroxide (10 g/L) TS and heat the mixture in a water bath at 85°C for 15 minutes.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peak due to atazanavir (retention time about 22 minutes) and the peak with a relative retention of about 1.2 is at least 4.

Inject alternatively 20 µL each of solutions (1) and (2).

In the chromatograms obtained with test solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- 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

Either test A or test B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (150 mm × 4.6 mm) packed with end-capped base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm).

As the mobile phase use a solution prepared as follows: 60 volumes of acetonitrile R and 40 volumes of 0.02 M phosphate buffer pH 3.5. Prepare the 0.02 M phosphate buffer pH 3.5 according to the procedure described in the related substances test.

Prepare the following solutions using as diluent a mixture of equal volumes of acetonitrile R and water R. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity equivalent to 20.0 mg of atazanavir, accurately weighed, into a 20 mL volumetric flask. Add about 10 mL of the diluent, sonicate for about 10 minutes, allow to cool to room temperature and make up to volume. Filter a portion of this solution, discarding the first few mL. Dilute 5.0 mL of the filtrate to 50.0 mL with the diluent. For solution (2) use 0.11 mg of atazanavir sulfate RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C.

Inject alternately 20 µL each of solutions (1) and (2) and record the chromatograms for 1.5 times the retention time of atazanavir (about 4 minutes).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of atazanavir, (C_{38}H_{52}N_{6}O_{7}) in the capsules, using the declared content of C_{38}H_{52}N_{6}O_{7} in atazanavir sulfate RS.

B. Weigh and mix the contents of 20 capsules. Transfer a quantity equivalent to 20 mg of atazanavir, accurately weighed, to a 20 mL volumetric flask. Add about 10 mL of methanol R, sonicate for about 10 minutes, allow to cool to room temperature and make up to volume with methanol R. Filter a portion of this solution, discarding the first few mL of the filtrate. Dilute 1.0 mL of the filtrate to 10.0 mL with methanol R. Measure the absorbance (1.6) of a 1 cm layer of this solution in at the maximum at about 250 nm, using methanol R as a blank. Calculate the percentage content of C_{38}H_{52}N_{6}O_{7} in the capsules using an absorptivity value of 14.5 for atazanavir sulfate (\text{A}_{1% cm} = 145). Each mg of atazanavir sulfate (C_{38}H_{52}N_{6}O_{7} \cdot H_{2}SO_{4}) is equivalent to 1.139 mg of atazanavir (C_{38}H_{52}N_{6}O_{7}).

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Daclatasvir dihydrochloride
(*Daclatasviri dihydrochloridum*)

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/18.762, May 2018). The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality_safety/quality_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

**[Note from the Secretariat.](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects) The monograph on Daclatasvir dihydrochloride is proposed for inclusion in The International Pharmacopoeia. The methods and specifications were drafted based on information provided by manufacturers and found in the scientific literature and on laboratory investigations.]**

**Molecular formula.** C\textsubscript{40}H\textsubscript{50}N\textsubscript{8}O\textsubscript{6}·2HCl

**Relative molecular mass.** 811.81

**Graphic formula**

![Graphic formula of Daclatasvir dihydrochloride](image-url)

**Chemical name.** Methyl N-\((2S)-1-[(2S)-2-[5-[4-[(2S)-1-[(2S)-2-[(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl]phenyl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate dihydrochloride; CAS Reg. No. 1009119-65-6

**Description.** A white to a pale yellow powder.

**Solubility.** Freely soluble in water, soluble in methanol and very slightly soluble in dimethylformamide.

**Category.** Antiviral (nonstructural protein 5A inhibitor).

**Storage.** Daclatasvir dihydrochloride should be kept in a tightly closed container.

**Additional information.** Daclatasvir dihydrochloride may exhibit polymorphism.

**Requirements**

**Manufacture.** The production method is validated to demonstrate that genotoxic halogenated biphenyl derivatives are adequately controlled in the final product.
Definition. Daclatasvir dihydrochloride contains not less than 97.0% and not more than 102.0% ("Assay", method A) or not less than 98.0% and not more than 102.0% ("Assay", method B) of \( \text{C}_{40}\text{H}_{50}\text{N}_{8}\text{O}_{6} \cdot 2\text{HCl} \), calculated with reference to the anhydrous substance.

Identity tests

- Either tests A, E and F or tests D, E and F together with any one of tests B or C may be applied.

A. 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 daclatasvir dihydrochloride RS or with the reference spectrum of daclatasvir dihydrochloride.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and daclatasvir dihydrochloride RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from daclatasvir dihydrochloride RS.

B. Carry out the test as described under 1.14.4 High-performance-liquid chromatography using the conditions given under “Assay”, method A. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to daclatasvir in the chromatogram obtained with solution (2).

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

C.1 Carry out test as described under 1.14.1 Thin-layer chromatography using silica gel R4 or similar as the coating substance and a mixture of 77 volumes of ethyl acetate R, 15 volumes of methanol R and 8 volumes of water R as the mobile phase. Apply separately to the plate 2 \( \mu \text{L} \) of each of the following 2 solutions in methanol R containing (A) 10 mg of the test substance per mL and (B) 10 mg of daclatasvir dihydrochloride RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of cool air. Examine the chromatogram in ultraviolet light (365 nm).

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

C.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described above under C.1. After drying the plate spray with basic potassium permanganate (5 g/L) TS. Examine the chromatogram in daylight.

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

D. The absorption spectrum (1.6) of a 10 \( \mu \text{g} \) per mL solution of the test substance in methanol R, when observed between 230 nm and 400 nm, exhibits one maximum at 314 nm.

E. Determine the specific optical rotation (1.4) using a 10 mg per mL solution of the test substance in methanol R. Calculate with reference to the anhydrous substance: \( [\alpha]_{D}^{25} = -92.0 \) to -102.0.
F. Dissolve 20 mg of the test substance in 20 mL methanol R; the solution yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

**Sulfated ash** (2.3). Not more than 1.0 mg/g.

**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 metals content according to method A; not more than 20 μg/g.

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using 0.2000 g of the substance; the water content is not more than 10 mg/g.

**pH value.** pH of a 10 mg/mL solution, 2.5–3.5

**Impurity A (daclatasvir enantiomer).** Carry out test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded cellulose *tris* (3,5-dichlorophenyl carbamate) (3 μm).¹ As mobile phase use a mixture of 30 volumes of 1.58 g per litre ammonium bicarbonate R in water and 70 volumes of acetonitrile R.

Operate at a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 320 nm. Maintain the column temperature at 40°C.

Prepare the following solutions in mobile phase. For solution (1) dissolve 25.0 mg of the test substance in 50.0 mL. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL. Dilute 2.0 mL of this solution to 100.0 mL. For solution (3) use a solution containing 0.01 mg daclatasvir impurity A and 0.01 mg daclatasvir dihydrochloride RS per mL.

Inject 10 μL of solution (3). The test is not valid unless the resolution factor between the peaks due to daclatasvir (retention time about 4.5 minutes) and impurity A (daclatasvir enantiomer) (relative retention of about 1.6) is at least 3.0.

Inject alternately 10 μL of solutions (1) and (2).

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A (daclatasvir enantiomer) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography.

Use the following conditions for gradient elution:

- mobile phase A: 0.1% (v/v) solution of trifluoroacetic acid R;
- mobile phase B: a mixture of 30 volumes of methanol R and 70 volumes of acetonitrile R.

¹ A Lux i-Cellulose-5 column or a Chiralpak IC-3 column were found suitable.
Operate at a flow rate of 1.0 mL/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 304 nm. Maintain the column at a temperature of 40°C.

Prepare the following solutions using as diluent a mixture of 80 volumes of mobile phase A and 20 volumes of mobile phase B. For solution (1) dissolve 25.0 mg of the substance to be examined and dilute to 50.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 5.0 mL of this solution to 50.0 mL. For solution (3) use a solution containing 0.5 mg of daclatasvir for peak identification RS (containing daclatasvir and the impurities B, D, F, G, H and I) per mL.

Inject alternatively 10 µL of solutions (1), (2) and (3).

Use the chromatogram obtained with solution (3) and the chromatogram supplied with daclatasvir for peak identification RS to identify the peaks due to the impurities B, D, F, G, H and I in the chromatogram obtained with solution (1). The test is not valid unless the peak-to-valley ration (Hp/Hv) is at least 20, where Hp is the height above the extrapolated baseline of the peak due to the co-eluting impurities B and C and Hv is the height above the extrapolated baseline at the lowest point of the curve separation the peak due to daclatasvir from the peak due to the co-eluting impurities B and C. The impurities, if present, are eluted at the following relative retentions with reference to daclatasvir (retention time about 17 minutes): impurity I about 0.21; impurity H about 0.62; impurity G about 0.76; impurities B and C about 1.12; impurity E about 1.16; impurity D about 1.22; impurity J about 1.39; impurity K about 1.66; and impurity F about 1.82.

In the chromatogram obtained with solution (1):

- the sum of the areas of any peak corresponding to impurities B and C (impurities B and C may co-elute) is not greater than 1.5 times the area of the peak due to daclatasvir obtained with solution (2) (0.15%);
- the area of any peak corresponding to impurities I, H, G, D or F is not greater than 1.5 times the area of the peak due to daclatasvir obtained with solution (2) (0.15%);
- the area of any other impurity peak is not greater than the area of the peak due to daclatasvir obtained with solution (2) (0.10%);
- the sum of the areas of all impurity peaks is not greater than 10 times the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.5 times the area of the peak due to daclatasvir obtained with solution (2) (0.05%).
**Assay**

- Either method A or method B may be applied.

**A.** Carry out test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (15 cm x 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 µm).²

Use the following conditions for gradient elution:

- **Mobile phase A:** 0.1 % (v/v) solution of trifluoroacetic acid R;
- **Mobile phase B:** a mixture of 50 volumes of methanol R and 50 volumes of acetonitrile R.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>70</td>
<td>30</td>
<td>Isocratic</td>
</tr>
<tr>
<td>1–13</td>
<td>70 to 60</td>
<td>30 to 40</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>13–16</td>
<td>60 to 15</td>
<td>40 to 85</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>16–18</td>
<td>15</td>
<td>85</td>
<td>Isocratic</td>
</tr>
<tr>
<td>18–20</td>
<td>15 to 70</td>
<td>85 to 30</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>20–25</td>
<td>70</td>
<td>30</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate at a flow rate of 1.0 mL/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 304 nm. Maintain the column at a temperature of 40°C.

Prepare the following solutions using as diluent a mixture of 70 volumes of mobile phase A and 30 volumes of mobile phase B.

For solution (1) dissolve 25.0 mg of the substance to be examined and dilute to 50.0 mL. Dilute 10.0 mL of this solution to 50.0 mL. For solution (2) dissolve 25.0 mg of daclatasvir dihydrochloride RS and dilute to 50.0 mL. Dilute 10.0 mL of this solution to 50.0 mL.

Inject alternately 20 µL each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of daclatasvir dihydrochloride (C₄₀H₅₀N₈O₆·2HCl) using the declared content of C₄₀H₅₀N₈O₆·2HCl in daclatasvir dihydrochloride RS.

**B.** Dissolve about 0.3 g, accurately weighed, in 5 mL water and add 20 mL of ethanol (~750 g/L) TS. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 40.59 mg of C₄₀H₅₀N₈O₆·2HCl.

---

² An XBridge C18 column or a Zorbax SB C18 column were found suitable.
Impurities

A. Methyl N-[(2R)-1-[(2R)-2-[5-[4-[(2R)-1-[(2R)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl]phenyl]phenyl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (daclatasvir enantiomer) (synthesis-related impurity)

B. Methyl N-[(2R)-1-[(2S)-2-[5-[4-[(2S)-1-[(2S)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl]phenyl]phenyl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (RSSS diastereomer) (synthesis-related impurity)

C. Methyl N-[(2S)-1-[(2R)-2-[5-[4-[(2S)-1-[(2S)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl]phenyl]phenyl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (SRSS diastereomer) (synthesis-related impurity)
D. Methyl \(N\)-[(2R)-1-[(2S)-2-[5-4’-2-[(2S)-1-[(2R)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl]phenyl]phenyl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (RSSR diastereomer) (synthesis-related impurity)

E. Methyl \(N\)-[(2S)-1-[(2S)-2-[5-4’-2-[(2S)-1-[(2S)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1H-imidazol-5-yl]phenyl]phenyl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl]carbamate (synthesis-related impurity)

F. Methyl [(2S)-1-[(2S)-2-5-4’-2-[(2S)-1-[(2S)-2-(methoxycarbonyl)amino]-3-methylbutanoyl]pyrrolidin-2-yl]-1,3-oxazol-5-yl]biphenyl-4-yl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (synthesis-related impurity)

G. Methyl [(2S)-1-[(2S)-2-5-4’-2-(2S)-1-acetylpyrrolidin-2-yl]-1H-imidazol-5-yl]biphenyl-4-yl]-1H-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (synthesis-related impurity)
H. Methyl((1S)-1-(((2S)-2-((4′-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (synthesis-related impurity)

I. 5,5′-[1,1′-Biphenyl]-4,4′-diylbis[2-(2S)-2-pyrrolidinyl-1H-imidazole] (synthesis-related impurity)

J. (2S,2′S)-2,2′-([1,1′-biphenyl]-4,4′-diyl)di-1H-imidazole-5,2-diyl)bis-1-pyrrolidinecarboxylic acid 1,1′-bis(1,1-dimethylethyl) ester (synthesis-related impurity)

K. 4,4′-Diacetylbiphenyl (synthesis-related impurity)
Daclatasvir tablets
*(Daclatasviri compressi)*

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/18.763, May 2018). The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality_safety/quality_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

**Category.** Antiviral (Nonstructural protein 5A inhibitor)

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

**Labelling.** The designation of the container should state that the active ingredient is in the dihydrochloride form and the quantity should be indicated in terms of the equivalent amount of daclatasvir.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 30 mg and 60 mg daclatasvir.

**Requirements**

Comply with the monograph for Tablets.

**Definition.** Daclatasvir tablets contain Daclatasvir dihydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of daclatasvir (C₄₀H₅₀N₈O₆) stated on the label.

**Identity tests**

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

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

A.1. Carry out test as described under 1.14.1 *Thin-layer chromatography* using silica gel R6 or similar as the coating substance and a mixture of 77 volumes of ethyl acetate R, 15 volumes of methanol R and 8 volumes of water R as the mobile phase. Apply separately to the plate 2 μL of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets containing 50 mg of daclatasvir with 5 mL of methanol R and filter. For solution (B) use a solution containing 11 mg of daclatasvir dihydrochloride RS per mL methanol R. After removing the plate from the
Daclatasvir tablets (Ph. Int.)

chromatographic chamber allow it to dry in air or in a current of cool air. Examine the chromatogram in ultraviolet light (365 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with 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 text A.1. After drying the plate spray with basic potassium permanganate (5 g/L) TS. Examine the chromatogram in daylight.

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

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions and solutions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to daclatasvir in the chromatogram obtained with solution (2).

C. To a quantity of powdered tablets containing the equivalent of 10 mg daclatasvir add 40 mL methanol R, sonicate for 5 minutes, allow to cool to room temperature, dilute to 50 mL and filter. Dilute 1 mL of the filtrate to 20 mL with methanol R. The absorption spectrum (1.6) of the resulting solution, when observed between 230 nm and 400 nm, exhibits one maximum at 314 nm.

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium 500 mL of dissolution buffer pH 6.8 and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool down to room temperature.

If necessary, dilute a suitable volume of the filtrate with dissolution medium to obtain a solution containing 0.06 mg of daclatasvir per mL. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 314 nm, using the dissolution buffer as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of daclatasvir dihydrochloride RS in the dissolution buffer.

For each of the tablets tested calculated the amount of daclatasvir (C_{40}H_{50}N_{8}O_{6}) in the medium. Each mg of daclatasvir dihydrochloride is equivalent to 0.910 mg of daclatasvir.

Evaluate the results as described under 5.5 Dissolution test for solid oral dosage forms, Acceptance criteria. The amount of daclatasvir in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

Related substances. Carry out test as described under 1.14.4 High-performance liquid chromatography.

Use the following conditions for gradient elution:

- mobile phase A: 0.1% (v/v) solution of trifluoroacetic acid;
- mobile phase B: a mixture of 30 volumes of methanol R and 70 volumes of acetonitrile R.
Prepare the following solutions using as diluent a mixture of 80 volumes of mobile phase A and 20 volumes of mobile phase B.

For solution (1) transfer a quantity of the powdered tablets containing the equivalent of 25.0 mg of daclatasvir to a 40 mL volumetric flask. Add about 30 mL diluent and sonicate for 5 minutes, cool to room temperature and make up to the volume with the diluent and filter. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 5.0 mL to this solution to 50.0 mL. For solution (3) use a solution containing 0.5 mg of daclatasvir for peak identification RS (containing daclatasvir and the impurities B, D, F, G, H and I) per mL.

Inject alternatively 10 µL of solutions (1), (2) and (3).

Use the chromatogram supplied with daclatasvir for peak identification to identify the peaks due to the impurities H and G in the chromatogram obtained with solution (3). The test is not valid unless the peak-to-valley ration (Hp/Hv) is at least 20, where Hp is the height above the extrapolated baseline of the peak due to the co-eluting impurities B and C and Hv is the height above the extrapolated baseline at the lowest point of the curve separation the peak due to daclatasvir from the peak due to the co-eluting impurities B and C.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than 2 times the area of the peak due to daclatasvir in the chromatogram obtained with solution (2) (0.2%);
- the sum of all areas of all impurity peaks is not greater than 15 times the area of the peak due to daclatasvir obtained with solution (2) (1.5%). Disregard any peak with an area less than the area of the peak due to daclatasvir obtained with solution (2) (0.1%).

**Assay.** Carry out test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 µm).¹

Use the following conditions for gradient elution:

- mobile phase A: 0.1% (v/v) solution of trifluoroacetic acid;
- mobile phase B: a mixture of 50 volumes of methanol R and 50 volumes of acetonitrile R.

¹ An XBridge C18 column or a Zorbax SB C18 column were found suitable.
Daclatasvir tablets (Ph. Int.)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>0–1</td>
<td>70</td>
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<td>Isocratic</td>
</tr>
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<td>70 to 60</td>
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<td>Isocratic</td>
</tr>
<tr>
<td>18–20</td>
<td>15 to 70</td>
<td>85 to 30</td>
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<tr>
<td>20–25</td>
<td>70</td>
<td>30</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate at a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 304 nm. Maintain the column temperature at 40°C.

Prepare the following solutions using as diluent a mixture of 70 volumes of mobile phase A and 30 volumes of mobile phase B.

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing 100.0 mg of daclatasvir to a 100 mL volumetric flask. Add about 60 mL of diluent and sonicate for 5 minutes, cool to room temperature and make up to volume with diluent. Filter and dilute 5.0 mL of the filtrate to 50.0 mL. For solution (2) dissolve 55.0 mg of daclatasvir dihydrochloride RS and dilute to 50.0 mL. Dilute 5.0 mL of this solution to 50.0 mL.

Inject alternately 20 µL each of solutions (1) and (2).

Measure the areas of the peak responses corresponding to daclatasvir obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of daclatasvir (C_{40}H_{50}N_{8}O_{6}) in the tablets using the declared content of C_{40}H_{50}N_{8}O_{6}·2HCl in daclatasvir dihydrochloride RS. Each mg of daclatasvir dihydrochloride is equivalent to 0.910 mg of daclatasvir.

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the monograph on Daclatasvir dihydrochloride.

***
Polymorphism

This is a draft proposal of a chapter for The International Pharmacopoeia (Working document QAS/17.716/Rev.1, May 2018). The draft has been revised based on the comments received during the public consultation held in July–September 2017. The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat. It is proposed to publish the following chapter on Polymorphism in the Supplementary Information section under “Notes for guidance”.]

Introduction and terminology

The aim of this chapter is to provide a brief overview of:

- the terminology associated with crystal polymorphism;
- some analytical techniques commonly used to characterise polymorphs;
- the relevance of polymorphism for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs); and
- the control strategies for polymorphism employed by The International Pharmacopoeia.

APIs and excipients, in the solid phase, can be classified as either crystalline or non-crystalline solids or a mixture thereof. A crystalline structure implies that the structural units (i.e. the unit cells) are repeated in a long range order. The atoms and/or molecules of an amorphous solid, however, are arranged in a non-ordered, random system, such as in the liquid state, and do not possess a distinguishable crystal lattice. Amorphous solids are classified as non-crystalline solids.

Variation in the crystallization conditions (temperature, pressure, solvent, concentration, rate of crystallization, seeding of the crystallization medium, presence and concentration of impurities, etc.) may cause the formation of different forms.

When the crystalline structure of the same chemical compound (and atomic formula) exhibits two or more patterns of the repeated unit cells, these crystalline structures are called polymorphs and the phenomena is referred to as polymorphism. The difference in internal crystal structure could be attributed to differences in molecule packing arrangements and/or different molecular conformations. When a chemical element (e.g. sulfur) exists in different crystalline forms, it is referred to as allotropy, not polymorphism (1). Due to the identical chemical composition of the polymorphic substance it will have the same chemical behaviour in solution, irrespective in the form in which it is presented.

Crystals of the same chemical compound with the same internal structure may exhibit different external shapes or crystal habits.
Solvates are crystal forms containing stoichiometric or non-stoichiometric quantities of a solvent. When the solvent incorporated into the crystal structure of the compound is water, the molecular adduct formed is referred to as a hydrate. Solvation and hydration products are also sometimes referred to as pseudopolymorphs. However, the term “pseudopolymorphism” is ambiguous because of its use in different circumstances. It is therefore preferable to use only the terms “solvates” and “hydrates”.

Occasionally a compound of a given hydration/solvation state may crystallize into more than one crystalline form; an example of such a compound is nitrofurantoin. Nitrofurantoin can be crystallized as two monohydrate forms (Forms I and II) and two anhydrous forms (designated polymorphs α and β).

Crystal forms are said to be isostructural when they have the same overall crystal packing. Solvates, which have the same overall crystal packing, but differ only in the solvents included in their crystal structures, are termed isostructural solvates, e.g., hydrate and isopropanolate of hexakis(2,3,6-tri-O-acetyl)-α-cyclodextrin.

The term desolvated solvate (which includes hydrates) has been used to classify a compound that was originally crystallized as a solvate but when the incorporated solvent is removed the crystal lattice of the solvated and desolvated crystal lattices show no or only relatively small differences, for example, desolvated monohydrate of terazosin HCl.

Amorphous forms of APIs and excipients are of substantial interest because they are usually more soluble than their crystalline counterparts but are usually considered to be thermodynamically less stable. Solid-state properties of amorphous forms of the same chemical compound (i.e., thermal behaviour, solubility profile, etc.) may differ; this phenomenon is referred to as polyamorphism.

Traditionally polymorphic forms of an API are classified as either crystalline, amorphous or solvate and hydrate forms. Co-crystals are crystalline materials composed of two or more different molecules, typically an API and co-crystal formers (“conformers”) within the same crystal lattice that are associated by nonionic and noncovalent bonds. An example of a co-crystal is fluoxetine HCl/succinic acid co-crystal. Co-crystals are thus more similar to solvates, in that both contain more than one component in the lattice. However, for co-crystals the conformer is non-volatile.

Pharmaceutical co-crystals have gained considerable attention as alternative forms in an attempt to enhance the bioavailability, stability and processability of the API in the manufacturing process. Another advantage of co-crystals is that they generate a diverse array of solid state forms for APIs that lack ionisable functional groups, which is a prerequisite for salt formation. Guidance and reflection papers on the use and classification of pharmaceutical co-crystals have been published.

Characterization and thermodynamic stability of solid forms

Crystalline forms are characterized based on the differences of their physical properties. Table 1 lists some examples of the properties that may differ among different forms.
Table 1. Examples of physical properties that may differ among different forms

<table>
<thead>
<tr>
<th>1. Packing properties</th>
<th>3. Spectroscopic properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Molar volume and density</td>
<td>a. Electronic state transitions</td>
</tr>
<tr>
<td>b. Refractive index</td>
<td>b. Vibrational state transitions</td>
</tr>
<tr>
<td>c. Conductivity (electrical and thermal)</td>
<td>c. Nuclear spin state transitions</td>
</tr>
<tr>
<td>d. Hygroscopicity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Thermodynamic properties</th>
<th>4. Kinetic properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Melting and sublimation temperatures</td>
<td>a. Dissolution rate</td>
</tr>
<tr>
<td>b. Internal energy (i.e. structural energy)</td>
<td>b. Rates of solid state reactions</td>
</tr>
<tr>
<td>c. Enthalpy (i.e. heat content)</td>
<td>c. Stability</td>
</tr>
<tr>
<td>d. Heat capacity</td>
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<tr>
<td>e. Entropy</td>
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<tr>
<td>f. Free energy and chemical potential</td>
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<tr>
<td>g. Thermodynamic activity</td>
<td></td>
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<tr>
<td>h. Vapour pressure</td>
<td></td>
</tr>
<tr>
<td>i. Solubility</td>
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<table>
<thead>
<tr>
<th>5. Surface properties</th>
<th>6. Mechanical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Surface-free energy</td>
<td>a. Hardness</td>
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<tr>
<td>b. Interfacial tensions</td>
<td>b. Tensile strength</td>
</tr>
<tr>
<td>c. Habit (i.e. shape)</td>
<td>c. Compatibility, tableting</td>
</tr>
</tbody>
</table>

Table 2 summarizes some of the most commonly used techniques to study and/or classify different forms. These techniques are often complementary and it is indispensable to use several of them. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can also be used to provide unequivocal proof of polymorphism.(10)

Any technique(s) chosen to confirm the identity of the specific form(s) must be proven to be suitably specific for the identification of the desired form(s). Care must be taken in choosing the appropriate sample preparation technique, as heat generation or exposure to elevated pressure may trigger conversion between different forms.

Table 2. Examples of some techniques that may be used to study and/or classify different crystalline forms

1. X-ray powder diffraction
2. Single crystal X-ray diffraction
3. Microcalorimetry
4. Thermal analysis (1.2.1 melting point,* differential scanning calorimetry, thermogravimetry, thermomicroscopy)
5. Moisture sorption analysis
6. Microscopy (electronic and optical)
7. Solid-state nuclear magnetic resonance;
8. Solubility studies
9. Spectrophotometry: Spectrophotometry in the infrared region (1.7)* and Raman spectrophotometry
10. Intrinsic dissolution rate
11. Density measurement

* Methods currently employed by The International Pharmacopoeia
Polymorphism (Ph. Int.)

Using suitable analytical techniques, the thermodynamic stability of the forms should be investigated. The form with the lowest free energy is the most thermodynamically stable at a given temperature and pressure. The other forms are said to be in a metastable state. At normal temperature and pressure, a metastable form may remain unchanged or may change to a thermodynamically more stable form. In general the more stable the form the less soluble it is. Conversion to a thermodynamically more stable form, may cause changes in some of the physical properties (see Table 1) of the compound that may result in changes to other critical properties such as bioavailability, manufacturability (also referred to as processability), etc.

If there are several crystalline forms one form is thermodynamically more stable at a given temperature and pressure. A given crystalline form may constitute a phase that can reach equilibrium with other solid phases and with the liquid and gas phases.

If each crystalline form is the more stable within a given temperature range the change from one form to another is reversible and is said to be enantiotropic. The change from one phase to another is a univariate equilibrium so that at a given pressure this state is characterized by a transition temperature. However, if only one of the forms is stable over the entire temperature range, the change is irreversible or monotropic.(11)

Relevance of polymorphism for APIs and FPPs

Polymorphism of APIs and excipients are of interest as they may affect bioavailability, toxicity and processability. Also the thermodynamic stability of the form included in the FPP is considered important as environmental conditions may compromise the stability thereof. For formulations where the API is dissolved, attention has to be paid to supersaturation with regards to different forms. A formulation might not be supersaturated regarding a metastable polymorph but supersaturated with regards to the thermodynamically stable polymorph. Control of the form by the manufacturer may be required during the processing of APIs and excipients and during the manufacturing of a dosage form to ensure the correct physical characteristics thereof. The control of a specific form is especially critical in the areas where the bioavailability, stability or processability are directly impacted.(4)

The form of a readily soluble API that is incorporated into a solution, for example, an injection, an oral solution or eye drops, is normally non-critical (an exception to this statement might be if the concentration of the solution is such that it is close to the limit of solubility of one of the possible polymorphs – as mentioned above). Similarly, if an API is processed during the manufacturing process to obtain an amorphous form (e.g. hot melt extrusion, spray-dried dispersion, etc.), the original form is considered non-critical, as long as the processability is not influenced.

The form may be critical when the material is included in a solid dosage form or as a suspension in a liquid dosage form. In such cases the characteristics of the different polymorphs may affect the bioavailability or dissolution of the material. The polymorphic form of a biopharmaceutical classification system (BCS) class I or III API in a solid oral dosage form is normally non-critical in terms of dissolution rate or bioavailability as by definition it would be readily soluble, but confirmation thereof by the manufacturer, is recommended. The ICH Harmonised Tripartite Guideline on Specifications: Test procedures and acceptance criteria for
new drug substances and new drug products: Chemical substances Q6A, provides guidance on when and how polymorphic forms should be monitored.\(^4\)

The inclusion of potentially harmful solvents in the crystal lattice, which may render APIs or excipients to be toxic or harmful to patients (i.e. solvates), should also be suitably regulated and monitored by the manufacturer.

**Polymorphism in The International Pharmacopoeia**

Where a monograph indicates that a compound shows polymorphism this may be true crystal polymorphism, occurrence of solvates or occurrence of the amorphous form.

*The International Pharmacopoeia* controls the forms of a limited number of substances by restricting it to either:

- a single form, for example, carbamazepine API (Anhydrous Form III), mebendazole API (Form C); or
- by limiting the presence of unwanted forms, for example, chloramphenicol palmitate API (should contain at least 90% of polymorph B).

The control of forms specified in *The International Pharmacopoeia* may be achieved by:

- permitting no deviation from the infrared absorption spectrum of the reference substance prescribed (or reference spectrum supplied) – when the infrared absorption spectrum has been proven to be specific to the preferred form and able to distinguish the undesired form(s), for example, indomethacin API;
- restricting the melting point range, for example, phenobarbital API;
- recommending the use of any other suitable methods such as X-ray powder diffractometry, for example, carbamazepine tablets;
- limiting the incorporated solvent (in the case of solvates/hydrates) with a specific limit test, for example, nevirapine hemihydrate API.

When the infrared identification test is able to detect differences in forms for a specific compound (i.e. polymorphism may be present for this compound), but the control of a specific form is not required by the monograph, the user may be instructed to:

- recrystallize both the test substance and the specified reference substance, in the event where the infrared spectra are found to be not concordant, for example, fluconazole API; and/or
- dry the API and/or specified reference substance to ensure that both forms are in the anhydrous or dehydrated state, for example, nevirapine hemihydrate API.

Whenever the choice of a specific form is critical with regard to bioavailability and/or stability, the method of the manufacturer of the product must be validated to consistently yield the desired polymorph in the final product at release and over its shelf life. The monograph will include a statement under the heading “Manufacturing” to draw attention to the control of a specified form during manufacturing where control is known to be critical, for example, carbamazepine oral suspension.
Polymorphism (Ph. Int.)

It is the intention of *The International Pharmacopoeia* to extend the inclusion of explicit statements in monographs, where appropriate, as information on the occurrence of polymorphism becomes available. The Secretariat thus cordially invites the users of *The International Pharmacopoeia* and manufacturers to share any relevant information that could be included in the monographs.

**References**


***
1. **Background**

Several pharmacopoeias, including the European Pharmacopoeia, during the past years and months adopted revised monographs on water for injections (WFI) allowing production by non-distillation technologies.

Up until now, the production of WFI had been limited to distillation only in many countries. The monograph revisions in the context of several pharmacopoeias were the result of extensive consultations with stakeholders. They newly allow for production of WFI by a purification process equivalent to distillation such as reverse osmosis, coupled with appropriate techniques.

The Japanese Pharmacopoeia and the US Pharmacopeia, for example, allow for production of WFI by distillation or a purification process proven to be equal or superior to distillation, and by distillation or reverse osmosis followed by ultrafiltration, respectively.

In the European context, EDQM conducted a survey in 2010 to gather data on the use of non-distillation technologies for producing WFI and organized an expert workshop in March 2011. The revised monograph in the European Pharmacopoeia foresees that the use of non-distillation technologies for the production of WFI requires that notice is given to the supervisory authority of the manufacturer before implementation.

Any non-distillation technology for producing WFI should be equivalent in quality to that produced by distillation, where equivalence in quality does not simply mean compliance with a specification but also takes into account the robustness of the production method. This is why the ongoing general revision of Annex 1 “Manufacture of sterile medicinal products” to the European Union good manufacturing practices (GMP) guidelines will include new guidance on production methods for WFI. In order to ensure the necessary guidance is available for the newly revised European monograph implementation, a question-and-answer (Q&A) document was prepared by the GMP/GMDP Inspectors Working Group of the European Medicines Agency.
Inquiry regarding production of water for injections

2. WHO context

At an informal WHO consultation on good practices for health products manufacture and inspection held in April 2017, it was noted that new technologies were being adopted for the manufacture of WFI internationally, as outlined above. The monograph on “Water for injections” included in The International Pharmacopoeia and the GMP for water describe a distillation process only when used as WFI, whereas other technologies, such as reverse osmosis, have been included in other pharmacopoeias.

This was reported to the 52nd WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Expert Committee members noted the report and recommended that the WHO Secretariat should collect feedback on whether to revise the WHO specifications and GMP in relation to the production of WFI.

Within the context of the WHO publications the following contain information on the production of WFI by distillation only:

- WHO good manufacturing practices: water for pharmaceutical use (WHO Technical Report Series, No. 970, Annex 2, 2012);

In light of the above, feedback is being sought on whether the WHO specifications and GMP text(s):

- should be revised in relation to the production of WFI allowing other purification processes as well,
  - and if yes, if details on additional requirements should be added,
    - and if yes, which additional requirements should be added.

***
Proposal for revision of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

Working document QAS/18.768 (April 2018) relates to a proposed revision of the WHO Certification Scheme, a voluntary agreement among Member States to provide assurance about the quality of pharmaceutical products moving in international commerce. The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

1. Introduction
The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (the “Scheme”) is an international voluntary agreement to provide assurance, to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce. The primary document of the Scheme is the certificate of a pharmaceutical product (CPP).

The fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in 2017 was informed about the current situation of the Scheme, including the fact that the forty-third Expert Committee in 2008 had recommended that “the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be revised” in line with recent developments. The Expert Committee in 2017 recommended that the “WHO Secretariat should prepare a proposal for revision of the Scheme for public consultation”.

The objective of this working document is to compile key issues on the Scheme and provide a proposed revision of the Scheme for consideration during the upcoming fifty-third ECSPP meeting in 2018.

2. Background
The Scheme has been in operation since 1969 (World Health Assembly resolution WHA 22.50) and was amended in 1975 (WHA 28.65), 1988 (WHA 41.18), 1992 (WHA 45.29) and 1997 (WHA 50.3) (1–5). The current Scheme provides the following three types of certificate:
- CPP;
- statement of the licensing status of pharmaceutical product;
- batch certificate.

In 2007, the forty-second ECSPP discussed and identified a number of perceived problems with the operation of the Scheme (6).

In 2008, a WHO consultation was held to make recommendations for consideration during the forty-third ESPCC, taking account of the WHO working document QAS/07.240 which contains key issues and possible action (7). The forty-third ECSPP in 2008 discussed the report of the consultation (working document QAS/08.279) (8). In light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector, coupled with changes in the make-up of both the regulators and the groups involved in procurement, the
forty-third ECSPP endorsed the following recommendations (9):

1. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be revised;
2. The proposal for revision of the Scheme and modification of the guidelines should be discussed by the relevant WHO Governing Bodies – the Executive Board and the World Health Assembly – and in consultation with WHO’s Legal Counsel.
3. In the interim a question and answer (Q&A) paper should be prepared on the function of the Scheme.”

Based on the above recommendation, as an interim measure, a Q&A document on the function of the Scheme was developed in 2010 and it was revised in 2015 (10, 11). However, the Scheme itself has not been revised since 1997.

In 2017, the fifty-second ECSPP recommended that the “WHO Secretariat should prepare a proposal for revision of the scheme for public consultation” (12).

The draft working document which includes the proposed revision of the Scheme was prepared by the WHO Secretariat and it will be discussed during an informal consultation planned to be held on 19 to 20 May 2018. In addition, the draft working document will be circulated, including to the Member States and other interested parties, for public consultation to prepare a version of the working document for possible endorsement by the fifty-third ECSPP.

3. Proposed revision of the Scheme

Since the last revision of the Scheme in 1997 it has been discussed on various occasions and key issues and possible actions have been identified. These are roughly classified into the following two aspects:
(a) issues related to the revision of the Scheme;
(b) issues related to implementation/operational aspects of the Scheme.

The objective of this working document is to provide a proposed revision of the scheme for consideration [endorsement/adoption] during the upcoming fifty-third ECSPP. Therefore, possible action related to implementation and operational aspects of the Scheme (e.g. promotion of the Scheme, making use of IT) would be considered after adoption of the revision of the Scheme.

3.1 Summary of key issues and proposed actions related to the revision of the Scheme

The table below outlines key issues and possible actions. These were prepared mainly based on the report of the forty-third ECSPP and on working documents QAS/07.240 and QAS/08.279 and the Q&A document\(^1\) as well as comments from the Member States and interested parties during public consultation (6, 7, 9, 12).

\(^1\) Q16 is “What are the main problem encountered in the application of the Scheme”

<table>
<thead>
<tr>
<th>Key issues</th>
<th>Proposed actions</th>
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<tbody>
<tr>
<td>The Scheme is formally at present directed to individual Member States, whereas regulatory and procurement groupings of multistate organizations also need to be able to operate within the Scheme; this applies to both issuing and receiving parties</td>
<td>The wordings in the Scheme should be changed so that regional organizations such as the European Union can formally participate in the Scheme</td>
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[Note from Secretariat: Member State(s)" => “Member State(s) and/or regional authority(ies)".]

(Continued)
## Proposal for revision of the WHO Certification Scheme

### Key issues

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<tr>
<td><strong>b</strong></td>
<td>The list of competent authorities is out of date; details of some authorities have changed. The current list of countries that participate in the Scheme in its present form is not readily available</td>
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<tr>
<td><strong>c</strong></td>
<td>Exporting countries that do not fulfil the prerequisites required by the Scheme issue certificates to support export</td>
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<tr>
<td><strong>d</strong></td>
<td>The CPP is no longer provided to substitute the full dossier quality safety and efficacy (QSE) review</td>
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<td><strong>e</strong></td>
<td>Information on who released the batch for marketing is not disclosed in certificates issued by exporting countries</td>
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<td><strong>f</strong></td>
<td>There have been cases in which forged certificates have been supplied to competent authorities of importing countries</td>
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<td><strong>g</strong></td>
<td>Lead times of the certifying authorities can be very long, sometimes several months</td>
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<td><strong>h</strong></td>
<td>Importing countries require legalization of certificates, additional stamps, etc.</td>
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### Proposed actions

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<td><strong>b</strong></td>
<td>Memberships as “certificate-issuing” countries should be renewed every five years</td>
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<td></td>
<td>[Note from Secretariat: Added new para. as section 2.5; See below for more detail.]</td>
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<td></td>
<td>Member States should inform any update of the name and address of competent authorities to the WHO secretariat</td>
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<td></td>
<td>[Note from Secretariat: Added new paragraph as section 2.7.]</td>
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<tr>
<td><strong>c</strong></td>
<td>Memberships as “certificate-issuing” countries should be renewed every five years. Member States intending to continue to participate in the Scheme as “certificate-issuing” countries should resubmit notification to the Director-General of the World Health Organization (WHO) in the same way as section 2.1</td>
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<tr>
<td></td>
<td>[Note from Secretariat: Added new paragraph as section 2.5.]</td>
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<td>Member States intending to participate in the Scheme as certificate-issuing countries should declare that the competent authority meets the requirements in the notification to the WHO Director-General</td>
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<td></td>
<td>[Note from Secretariat: Added new paragraph as section 2.4.]</td>
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<td></td>
<td>In case that WHO does not receive the notification for renewal of membership for a long time period, the Director-General may delete such a Member State’s name from the participant list in consultation with the relevant Expert Committee</td>
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<td>[Note from Secretariat: Added new paragraph as section 2.8.]</td>
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<td><strong>d</strong></td>
<td>CPPs should not be requested in countries that have the capability to conduct full QSE reviews</td>
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<td>[Note from Secretariat: Added new paragraph as section 2.6.]</td>
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<td><strong>e</strong></td>
<td>The certificate should include batch release site information in the CPP as a new option (in section 2A.3, explanatory note 8 in model certificate of the guidelines) (“option c” will become the new “d” and a new “c” will be created)</td>
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<td>[Note from Secretariat: Added new words in Appendix 1 of the Annex.]</td>
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<td><strong>f</strong></td>
<td>Email address, telephone and fax numbers should be provided as contact information so that the requesting authority can request confirmation to the certifying authority countries easily</td>
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<td></td>
<td>[Note from Secretariat: Added new words in section 2.4.]</td>
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<td><strong>g</strong></td>
<td>Certifying authority should provide a certificate without undue delay</td>
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<td></td>
<td>[Note from Secretariat: Added new paragraph as section 4.10.]</td>
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<td><strong>h</strong></td>
<td>Unnecessary legalization should not be requested</td>
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<td></td>
<td>[Note from Secretariat: Added new paragraph as section 4.7.]</td>
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</table>
3.2 Proposed revision of the Scheme

The proposal for revision of the Scheme is attached as an annex. The amendments of the Scheme in the annex are presented in tracked-change mode. Moreover, it should be noted that this revision includes not only an amendment related to 3.1 in this working document but also editorial changes such as:

- updating some definitions in “Glossary and index” in conformity with latest version of relevant guidelines;
- replacing some words (e.g. “license” by “market authorization”).

4. Other issues related to operation of the Scheme

The table below outlines key issues not related to revision of the Scheme. As described in section 3 of this document, possible actions regarding implementation/operation of the Scheme (e.g. promotion of the Scheme, making use of IT) should be considered after adoption of the revision of the Scheme.

<table>
<thead>
<tr>
<th>Key issues</th>
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<tbody>
<tr>
<td>a Countries not party to the Scheme issue certificates to support export of pharmaceutical products.</td>
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<tr>
<td>b Not all of certificate-issuing countries adhere to the WHO template</td>
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<tr>
<td>c Member States issue certificates for products not manufactured under their jurisdiction, e.g. for products not authorized for marketing in their countries or not manufactured in their country.</td>
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<tr>
<td>d Exporting countries issue other certificates such as free sale certificates.</td>
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<tr>
<td>e There are inconsistencies in listing the trade name of the product in the recipient country, if different from the certifying country.</td>
</tr>
<tr>
<td>f The way of applying for a CPP is not harmonized, with each certifying authority having its own system. (It would be helpful to work towards regional harmonization and a standard electronic submission.)</td>
</tr>
</tbody>
</table>

5. References

2. World Health Assembly resolution WHA28.65 (1975).
3. World Health Assembly resolution WHA41.18 (1988).
5. World Health Assembly resolution WHA50.3 (1997).
10. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Question and Answer (Q&A) (QAS/10.374, 2010)
11. WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce: Questions and Answers (Q & A) (WHO Drug Information Vol. 30, No. 3, 2016)
Consultation documents

Proposal for revision of the WHO Certification Scheme

Annex

[Note from Secretariat: In the online document posted for comment, the new text based on proposed action on the preceding pages is presented in tracked-change mode.]

Guidelines on the implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

1. Provisions and objectives
1.1 A comprehensive system of quality assurance must be founded on a reliable system of marketing authorization and independent analysis of the finished pharmaceutical product, as well as upon assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as good manufacturing practices (GMP).

1.2 In 1969, the Twenty-second World Health Assembly, by resolution WHA22.50, endorsed requirements for Good Practices in the Manufacture and Quality Control of Drugs (1) (referred to henceforth as “GMP as recommended by WHO”). These comprise internationally-recognized and respected standards that all Member States are urged to adopt and to apply. These requirements have since been revised several times.

1.3 These standards provide the basis for the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (referred to henceforth as “the Scheme”) recommended initially in resolution WHA22.50 (1). The Scheme is an administrative instrument that requires each participating Member State or regional authority, upon application by a commercially interested party, to attest to the competent authority of another participating Member State or regional authority that:

• a specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;

• the plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by the World Health Organization (WHO)); and

• all submitted product information, including labelling, is currently authorized in the certifying country.

1.4 The Scheme, as amended in 1975 (2), 1988 (3), 1992 (4) and 1997 (5), by resolutions WHA28.65, WHA41.18, WHA45.29 and WHA50.3, is applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals.

1.5 Provision for certification of active pharmaceutical ingredients (APIs) is also included within the scope of the Scheme. This will be the subject of separate guidelines and certificates.

2. Membership

[Note from Secretariat: the new text in section 2 includes rearrangement of the order of paragraphs and such change is NOT presented in tracked-change mode in the online document posted for comment, except for the section number.]

2.1 Any Member State as well as regional authority that has legal right to control the regulation of pharmaceutical products are eligible to participate in the Scheme as a certifying member and/or a requesting member if it complies with the requirements stipulated in section 2.2 or 2.3.

2.2 A Member State intending to become a certifying member should possess:

• an effective marketing authorization system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;

• GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;

• effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country, including access to an independent quality control laboratory;

• a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;
Proposal for revision of the WHO Certification Scheme

- administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.

2.3 A regional authority intending to become a certifying member should possess by itself or through its legal framework:
- an effective marketing authorization system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;
- GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;
- effective controls to monitor the quality of pharmaceutical products registered or manufactured within its region, including access to an independent quality control laboratory;
- a pharmaceuticals inspectorate, operating as an arm of the drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;
- administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State and regional organization known to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.

2.4 Membership as a certifying member and/or requesting member can be applied by notifying in writing to the WHO Director-General of:
- its willingness to participate in the Scheme as a certifying member and/or a requesting member (Member States and regional authorities may participate only as a certifying member to control the import of pharmaceutical products and APIs);
- any significant reservations it intends to observe relating to this participation;
- the name and address (including email address, telephone and fax numbers) of its drug regulatory authority or other competent authority; and
- declaration to comply with the requirements for a certifying member stipulated in section 2.2 or 2.3, if applicable.

2.5 A Member State and regional authority that has a membership of a certifying member should resubmit the notification in section 2.4 at least once every five years, in order to ensure that it continues to comply with the requirement stipulated in section 2.2 or 2.3 and that contact information keeps updated.

2.6 Consolidated list of information on the notification submitted by Member States and regional authorities in accordance with provision in sections 2.4, 2.5 and 2.7 will be available through WHO’s official website (see also section 3.3).

2.7 A Member State and regional authority should inform WHO of any change of information notified to the WHO Director-General.

2.8 Membership as a certifying member may be disqualified by the Director-General after consultation with the ECSPP in the case that a Member State or regional authority would fail to resubmit a notification in accordance with provision in section 2.5 for a long period.

2.9 Each Member State and regional authority assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision, under any circumstance, for external inspection or assessment, either of a competent national authority or of a manufacturing facility. However, should a Member State or regional organization so wish, it could approach WHO, or a well-recognized drug regulatory authority, to occasionally delegate consultants to act as advisers in the course of national inspections and inspector training activities.

3. Requesting a certificate

3.1 Three documents can be requested within the scope of the Scheme:
- a certificate of a pharmaceutical product (product certificate);
- a statement of licensing status of pharmaceutical product(s); and
- a batch certificate of a pharmaceutical product.

3.2 Proposed formats for these documents are provided in Appendices 1, 2 and 3 of these guidelines. All participating Member States and regional authorities are henceforth urged to adopt these formats to facilitate interpretation of certified information. Requests for the provision of certificates offering
more limited attestations, for instance, that the manufacturer complies with GMP or that the product is authorized for “free sale” within the country of export are discouraged. Similarly, requests should not be made for certification of information going beyond the scope of this Scheme. When manufacture takes place in a country other than that from which the product certificate is issued, an attestation relevant to compliance of the manufacture with GMP may still be provided (as an attachment to the product certificate) on the basis of inspections undertaken for registration purposes.

The Explanatory Notes attached to the three documents referred to above are very important. Whilst they are not part of the document to be certified, they should always be attached to the certificate.

3.3 A list of addresses of competent national regulatory authorities participating in the Scheme that are responsible for the registration of pharmaceutical and/or veterinary products, together with details of any reservations they have declared regarding their participation in the Scheme will be available at the WHO official website as indicated in section 2.6.

3.4 Each competent authority in certifying members should issue guidelines to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the drug regulatory process and the circumstances in which each of the three types of documents will be required.

**Certificate of a pharmaceutical product**

3.5 The Certificate of a pharmaceutical product (Appendix 1) issued by the competent authority in the exporting country or regional authority (“the certifying authority”), is intended for use by the competent authority in an importing country and regional organization in two situations:

- when the product in question is under consideration for a marketing authorization that will authorize its importation and sale;
- when administrative action is required to renew, extend, vary or review such a marketing authorization.

3.6 The Certificate of a pharmaceutical product should not be required by the Member States or regulatory authorities where they undertake full quality, safety and efficacy review by themselves.

3.7 All requests for certificates should be channeled through the agent in the importing country (see section 3.4) and the marketing authorization holder or other commercially-interested party in the exporting country (“the applicant”). The applicant should submit the following information for each product to the authority issuing the certificate:

- name and dosage form of product
- name and amount of active ingredient(s) per unit dose (International Nonproprietary Name(s) where such exist(s)),
- name and address of marketing authorization holder and/or manufacturing facility,
- formula (complete composition including all excipients; also particularly when no marketing authorization exists or when the formulation differs from that of the authorized product),
- product information for health professionals and for the public (patient information leaflets) as approved by the certifying authority,

For product information to be attached to the certificate see section 4.7

3.8 The certificate is a confidential document. As such, it can be issued by the certifying authority only with the permission of the applicant and, if different, of the marketing authorization holder.

3.9 The certificate is intended to be incorporated into a marketing authorization application in the competent authority in the importing country and regional authority (“the requesting authority”). Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

3.10 When any doubt arises about the status or validity of a certificate, the requesting authority should request a copy directly from the certifying authority, as provided for under section 4.9 of these guidelines.

3.11 In the absence of any specific agreement, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.

3.12 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.

3.13 Supplementary attestations are obtainable only at the discretion of the certifying authority and with the permission of the applicant. The certifying authority is under no obligation to supply additional information. Requests for supplementary...
information should consequently be referred to the applicant, and only in exceptional circumstances to the certifying authority.

**Statement of marketing authorization**

3.14 Model statement of marketing authorization (Appendix 2). This attests only that a marketing authorization has been issued for a specified product, or products, for use in the exporting country. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and preparation of information. The importation of any product that is provisionally selected through this procedure should be determined on the basis of a CPP.

**Batch certificate**

3.15 A batch certificate of a pharmaceutical product (Appendix 3) refers to an individual batch of a pharmaceutical product and is a vital instrument in drug procurement. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.

3.16 A batch certificate is normally issued by the manufacturer and only exceptionally, as in the case of vaccines, sera and some other biological products, by the competent authority in the exporting country or regional authority. The batch certificate is intended to accompany and provide an attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already obtained market authorization in the importing country. The batch certificate should include the specifications of the final product at the time of batch release and the results of a full analysis undertaken on the batch in question. In most circumstances these certificates are issued by the manufacturer to the importing agent (i.e. the marketing authorization holder in the importing country), but they must be made available at the request of – or in the course of any inspection made on behalf of – the competent authority.

**4. Issuing a certificate**

4.1 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO emblem, but a statement should always be included to confirm whether or not the document is issued in the format recommended by WHO.

4.2 When the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:

- applies identical GMP standards to the production of all batches of pharmaceutical products manufactured within the facility, including those destined exclusively for export;
- consents, in the event of identification of a quality defect consonant with the criteria set out in section 5.1, to relevant inspection reports being released, in confidence, to the requesting authority, should the latter so require.

4.3 When the applicant is not the manufacturer of the finished dosage form, the certifying authority should similarly satisfy itself – in so far as it has authority to inspect the records and relevant activities of the applicant – that it has the applicant’s consent to release relevant reports on the same basis as described in section 4.2 (b) above.

4.4 GMP as recommended by WHO assigns to the manufacturer of the finished dosage form responsibility for assuring the quality of APIs. National or regional regulations may require that suppliers of APIs be identified in the marketing authorization, but the competent authority may have no power to inspect them.

4.5 Notwithstanding this situation, a certifying authority may agree, on a discretionary and voluntary basis, and at the request of a manufacturer, to undertake an inspection of a manufacturer of APIs to satisfy specific requirements of a requesting authority. Alternatively, pending the development of specific guidelines for APIs, the certifying authority may be able to attest that the manufacturer is an established supplier of the substance in question to manufacturers of finished dosage forms authorized for marketing under its jurisdiction.

4.6 Whenever a product is purchased through a broker or another intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the product for which the applicant is not directly responsible have been undertaken in compliance with GMP as recommended by WHO.

4.7 The certifying authority should officially stamp and date all copies of product information submitted to it in support of an application for a certificate and intended to be appended to the certificate.

Every effort should be made to ensure that certificates and all annexed documentation are
consonant with the version of the marketing authorization operative on the date of issue. Nevertheless, requesting authorities should not request unnecessary legalization procedure that may cause undue delay of certificates.

When available, the certifying authority will add a summary basis of approval or any other material the authority deems relevant. Translation by an applicant of these materials into a widely used language, preferably English, shall be deemed to satisfy the provision of 3.11.

4.8 Any additional attachment to a certificate submitted by the applicant, such as price lists of products for which bids are offered, should be clearly identified as not comprising part of the attestation made by the certifying authority.

4.9 To avert potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous and to enable the certifying authority to maintain comprehensive records of countries to which specific products have been exported, each certificate should identify the importing country and be stamped on each page with the official seal of the certifying authority.

If requested, an identical copy, clearly marked as duplicate, should be forwarded by the certifying authority on demand directly to the requesting authority.

4.10 The certifying authority should establish standard period of time for issue of certificates. It should endeavor to make each issue of certificate completed within this period as far as the applicant submits sufficient documents.

5. Notifying and investigating a quality defect

5.1 Each certifying authority undertakes to institute enquiries into any quality defect reported in a product exported in accordance with the provisions of the Scheme, on the understanding that:

- the complaint is transmitted, together with the relevant facts, through the requesting authority;
- the complaint is considered to be of a serious nature by the latter authority; and
- the defect, if it appeared after delivery of the product into the importing country, is not attributable to local conditions.

5.2 In the case of obvious doubt, a participating national authority may request WHO to assist in identifying an independent quality control laboratory to carry out tests for the purposes of quality control.

5.3 Each certifying authority undertakes to inform WHO and, as far as is possible, all competent national authorities, of any serious hazard newly associated with a product exported under the provisions of the Scheme or of any criminal abuse of the Scheme directed, in particular, to the export of falsely labelled, substandard or falsified pharmaceutical products. On receipt of such notification, WHO will transmit the message immediately to the competent authority in each Member State and regional organization.

5.4 WHO stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References


Appendix 1

Model Certificate of a Pharmaceutical Product

Certificate of a pharmaceutical product

This certificate conforms to the format recommended by the World Health Organization (WHO) (general instructions and explanatory notes attached)

No. of Certificate: _________________________________________________________________

Certifying member (certifying country): ______________________________________________

Requesting member (requesting country): _____________________________________________

1. Name and dosage form of the product:

1.1. Active ingredient(s) and amount(s) per unit dose:

For complete composition including excipients, see attached.

1.2. Is this product authorized to be placed on the market for use in the exporting country?

yes/no (key in as appropriate)

1.3. Is this product actually on the market in the exporting country?

yes/no/unknown (key in as appropriate)

If the answer to 1.2. is yes, continue with section 2A and omit section 2B.

If the answer to 1.2 is no, omit section 2A and continue with section 2B:

2.A.1. Number of marketing authorization and date of issue:

2.A.2. Marketing authorization holder (name and address):

2.A.3. Status of marketing authorization holder:

a/b/c/d (key in appropriate category as defined in note 8)

2.A.3.1. For categories b, c and d, the name and address of the manufacturer producing the dosage form is:

2.A.3.2. For categories d, the name and address of the manufacturer certifying the finished pharmaceutical product batch is:

2.A.4. Is a summary basis for approval appended? yes/no (key in as appropriate)

2.A.5. Is the attached, officially approved product information complete and consonant with the market authorization? yes/no/not provided (key in as appropriate)

2.A.6. Applicant for certificate, if different from licence holder (name and address):

2.B.1. Applicant for certificate (name and address):

2.B.2. Status of applicant: a/b/c/d (key in appropriate category as defined in footnote 8)
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2.B.2.1. For categories b, c and d the name and address of the manufacturer producing the dosage form is:

2.B.2.2. For categories d, the name and address of the manufacturer certifying the finished pharmaceutical product batch is:

2.B.3. Why is marketing authorization lacking?
not required/not requested/under consideration/refused (key in as appropriate)

2.B.4. Remarks:

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? yes/no/not applicable (key in as appropriate)

3.1. Periodicity of routine inspections (years):

3.2. Has the manufacture of this type of dosage form been inspected? yes/no (key in as appropriate)

3.3. Do the facilities and operations conform to GMP as recommended by WHO? yes/no/not applicable (key in as appropriate)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? yes/no (key in as appropriate)

Address of certifying authority:

Telephone number: Fax number:

Email address:

Name of authorized person:

Signature:

Stamp and date:

General instructions
Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

1 This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2 Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

3 The formula (complete composition) of the dosage form should be given on the certificate or be appended.

4 Details of quantitative composition are preferred but their provision is subject to the agreement of the marketing authorization holder.

5 When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the marketing authorization.
Sections 2A and 2B are mutually exclusive.

Indicate, when applicable, if the licence is provisional, or the product has not yet been approved.

Specify whether the person responsible for placing the product on the market:
(a) manufactures the dosage form;
(b) packages and/or labels a dosage form manufactured by an independent company;
(c) certifies the finished pharmaceutical product batch; or
(d) is involved in none of the above.

This information can only be provided with the consent of the marketing authorization holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the marketing authorization. If the production site is changed, the marketing authorization has to be updated or it is no longer valid.

This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

This refers to product information approved by the competent national drug regulatory authority, such as summary product characteristics.

In this circumstance, permission for issuing the certificate is required from the marketing authorization holder. This permission has to be provided to the authority by the applicant.

Please indicate the reason that the applicant has provided for not requesting registration.
(a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases – not endemic in the country of export;
(b) the product has been reformulated with a view to improving its stability under tropical conditions; the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
(c) the product has been reformulated to meet a different maximum dosage limit for an active ingredient; any other reason, please specify.

Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.

The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

This section is to be completed when the marketing authorization holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.
Appendix 2

Model Statement of Marketing Authorization Status of Pharmaceutical Product(s)

No. of Statement: ________________________________

Certifying member (certifying country): ________________________________

Requesting member (requesting country): ________________________________

Statement of marketing authorization of pharmaceutical product(s) ¹

This statement indicates only whether or not the following products are licensed to be put on the market in the exporting country.

Applicant (name/address): ____________________________________________

<table>
<thead>
<tr>
<th>Name of product</th>
<th>Dosage form</th>
<th>Active ingredient(s)² and amount(s) per unit dose:</th>
<th>Marketing authorization no. and date of issue³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The certifying authority undertakes to provide, at the request of the applicant (or, if different, the marketing authorization holder), a separate and complete certificate of a pharmaceutical product (CPP) in the format recommended by the World Health Organization (WHO), for each of the products listed above.

Address of certifying authority: ____________________________________________

Telephone number: __________________ Fax number: __________________

Email address: __________________

Name of authorized person: ____________________________________________

Signature: ____________________________________________________________

Stamp and date: ________________________________________________________

This statement conforms to the format recommended by WHO.

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

¹ This statement is intended for use by importing agents who are required to screen bids made in response to an international tender and should be requested by the agent as a condition of bidding. The statement indicates that the listed products are authorized to be placed on the market for use in the exporting country. A CPP in the format recommended by WHO will be provided, at the request of the applicant and, if different, the marketing authorization holder, for each of the listed products.

² Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

³ If no marketing authorization has been granted, enter “not required”, “not requested”, “under consideration” or “refused” as appropriate.
Appendix 3

Model Batch Certificate of a Pharmaceutical Products

Manufacturers/Official1 Batch Certificate of a Pharmaceutical Product

This certificate conforms to the format recommended by the World Health Organization (WHO) (general instructions and explanatory notes attached).

1. No. of Certificate:

2. Importing (requesting) authority:

3. Name of product:

3.1 Dosage form:

3.2 Active ingredient(s)2 and amount(s) per unit dose:

3.2.1 Is the composition of the product identical to that registered in the country of export? (yes/no/not applicable)3

If no: please attach formula (including excipients) of both products.

4. Marketing authorization holder4 (name and address):

4.1 Marketing authorization number4:

4.2 Date of issue4:

4.3 Marketing authorization issued by4:

4.4 Product certificate number4,5:

5.1 Batch number:

5.2 Date of manufacture:

5.3 Shelf life (years):

5.4 Contents of container:

5.5 Nature of primary container:

5.6 Nature of secondary container/wrapping:

5.7 Specific storage conditions:

5.8 Temperature range:

6. Remarks6:

7. Quality analysis:

7.1 What specifications apply to this dosage form. Either specify the pharmacopoeia or append company specifications.7

7.1.1 In the case of a product registered in the exporting country, have these company specifications7 been accepted by the competent authority? (yes/no)
7.2 Does the batch comply with all parts of the above specifications?
   yes/no (key in as appropriate)

7.3 Append certificate of analysis

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person: __________________________________________
   __________________________________________
   __________________________________________
   Telephone number: __________________ Fax number: __________________
   Email address: __________________________________________

Name of authorized person: __________________________________________
Signature: __________________________________________
Stamp and date: __________________________________________

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

Certification of individual batches of a pharmaceutical product is only undertaken exceptionally by the competent authority of the exporting country. Even then, it is rarely applied other than to vaccines, sera and biologicals. For other products, the responsibility for any requirement to provide batch certificates rests with the marketing authorization holder in the exporting country. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the competent authority in the exporting country. A copy should be sent to the marketing authorization holder.

1 Strike out whichever does not apply.
2 Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
3 “Not applicable” means that the product is not registered in the country of export.
4 All items under 4 refer to the marketing authorization or the certificate of a pharmaceutical product (CPP) issued in the exporting country.
5 This refers to the CPP as recommended by WHO.
6 Indicate any special storage conditions recommended for the product as supplied.
7 For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.
8 Identify and explain any discrepancies from specifications. Government batch release certificates issued by certain governmental authorities for specific biological products provide additional confirmation that a given batch has been released, without necessarily giving the results of testing. The latter are contained in the manufacturer’s certificate of analysis.
Appendix 4
Glossary and index

In order to facilitate understanding, this glossary explains terms in the guidelines and/or refers to relevant sections. It is considered as supplementary information and not as being a formal part of the Scheme.

- **abuse of Scheme.** See section 4.9 and 5.2 of the guidelines.
- **active pharmaceutical ingredients.** Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
- **addresses of competent authorities.** See item 2.6 and 3.3 of the guidelines.
- **applicant.** The party applying for a product certificate. This is normally the marketing authorization holder. In all instances, having regard to commercial confidentiality of certain data, the competent authority in the exporting country must obtain permission to release these data from the marketing authorization holder, or, in the absence of a marketing authorization, from the manufacturer.
- **authentication of certificates.** See section 4.9 of the guidelines.
- **batch (or lot).** A defined quantity of a starting material, packaging material, or product processed in a single process or series of processes so that it can be expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quality or as the amount produced in a final time interval.
- **batch certificate.** A document containing information, as set out in Annex 3 of the guidelines for use, will normally be issued for each batch by the manufacturer. Furthermore, exceptionally a batch certificate may be validated or issued by the competent authority of the exporting country, particularly for vaccines, sera and other biological products. The batch certificate travels with every major consignment (see also section 3.14 of the guidelines).
- **batch number (or lot number).** A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.
- **bulk product.** Any product that has completed all processing stages up to, but not including, final packaging.
- **certifying authority.** This is the competent authority that issues product certificates. It shall ensure that it possesses the capacities listed in section 2.2 and 2.3 of the guidelines.
- **charges for product certificates.** See section 3.11 of the guidelines.
- **competence and evaluation of national authority.** See sections 2.2, 2.3, 2.9 and 4.2 of the guidelines.
- **competent authority.** This is the national or regional authority as identified in the formal letter of acceptance in which each Member State or regional authority informs WHO of its intention to participate in the Scheme. The competent authority can issue or receive certificates. The extent of participation should be indicated in the letter of acceptance. (see section 2.1 of the guidelines)

WHO makes available a continuously updated list of addresses of competent authorities and the specific conditions for participation (see section 2.6 of the guideline).

- **dosage form.** The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir, suppository.
- **drug regulatory authority.** A national or regional authority responsible for the registration of and other regulatory activities connecting pharmaceutical products.
**expiry date.** The date given on the individual container (usually on the label) of a product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf life to the date of manufacture.

**finished pharmaceutical product.** A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

**free sale certificate.** See section 3.2 of the guidelines.

**good manufacturing practices.** That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

**good manufacturing practices certificate.** See section 3.2 of the guidelines.

**importing agents.** guidelines for. See section 3.4 of the guidelines.

**International Nonproprietary Name (INN).** The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

**language of product certificates.** See section 3.10 of the guidelines.

**limits of certification by competent authority.** See section 3.12 and 4.8 of the guidelines.

**manufacture.** All operations of purchase of materials and products, production, quality control, release, storage, distribution of pharmaceutical products, and related controls.

**manufacturer.** A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals. (for categories of manufacturer, see Appendix 1, Explanatory Note No. 7).

**marketing authorization.** A legal document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf life and storage conditions and packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a “licence” or “product licence”.

**marketing authorization holder.** An individual or a corporate entity being in the possession of a marketing authorization of a pharmaceutical product.

**pharmaceutical product.** Any material and product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in exporting state and/or the importing state.

**product.** See pharmaceutical product.

**product certificate.** A document containing the information as set out in Appendix 1 of the guidelines that is validated and issued for a specific product by the competent authority of the exporting country or regional authority and intended for use by the competent authority in the importing country or – in the absence of such an authority – by the drug procurement authority (see also section 3.5 of the guidelines).

**product information.** This is the approved product information referred to in section 4.7 of the guidelines and item 2.A.5 of the product certificate. It normally consists of information for health professionals and the public (patient information leaflets) as approved in the exporting country, and when available, a data sheet or a summary of product characteristics approved by the drug regulatory authority.

**production.** All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.
Proposal for revision of the WHO Certification Scheme

registration. Any statutory system of approval required at national or regional level as a precondition for introducing a pharmaceutical product onto the market.

specifications. A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

statement of licensing status. See section 3.13 of the guidelines and Annex 2

summary basis of approval. This refers to the document prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed (see section 4.7 of the guidelines and explanatory note 9 of the product certificate contained in Annex 1).

Summary product characteristics (SPC). Product information as approved by the drug regulatory authority. The SPC serves as the basis for production of information for health personnel as well as for consumer information on labels and leaflets of medicinal products and for control of advertising (see also product information).

tenders and brokers. See section 4.6 of the guidelines.

transmission of product certificate. See section 3.8 and 4.9 of the guidelines.

validity of product certificate. See section 3.9 of the guidelines.

when to request a product certificate. See item 3.5 of the guidelines.

WHO responsibility. See item 5.4 of the guidelines.

References

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Other recent WHO consultation documents

The following new or revised guidelines have recently been posted for public comment on the WHO website (www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

Revision of WHO GMP for sterile pharmaceutical products – a joint EU, PIC/S, WHO project

Working document QAS/17.745, December 2017

The European Commission (EC), WHO and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), have jointly proposed a revised version of the guidelines on manufacture of sterile medicinal products. The document is subject to parallel public consultation by the three entities.

Good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms: Part 2. Interpretation of part 1 – GMP for HVAC systems.

Working document QAS/18.759, February 2018

This document represents Part 2 of the heating, ventilation and air-conditioning (HVAC) systems guidelines. It contains non-binding examples, drawings, technical representations and interpretation in support of Part 1 of the HVAC systems guidelines.

Guidelines on import procedures for pharmaceutical products (revision)

Working document QAS/18.773, May 2018

This is a revision of the WHO guidelines published in 1996. They are intended to promote efficiency in applying relevant regulations, to simplify the checking and handling of consignments of pharmaceutical products in international transit and to provide a basis for collaboration between all parties involved in importation of medicines.

Validation of computerized systems (Appendix 5 to Guidelines on Validation)

Working document QAS/16.667/Rev.1, May 2018

This is a revision of the 2006 WHO guidance on validation of computerized systems. It applies to systems used in good manufacturing practices (GMP) but may be extended to systems used in all good practice (GXP) activities, as appropriate.