MOXIFLOXACIN TABLETS
(MOXIFLOXACINI COMPRESSI)

Draft proposal for The International Pharmacopoeia
(March 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Herbert Schmidt, Medicines Quality Assurance Programme, Technologies, Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4856 or email: schmidth@who.int by 30 April 2019.

In order to speed up the process for receiving draft monographs and for sending comments, please send your email address to jonessi@who.int and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

Note from the Secretariat: The proposed monograph is based on information provided by the British Pharmacopoeia and pharmaceutical manufacturers, found in the scientific literature and on laboratory investigations.

The monograph is proposed for inclusion in The International Pharmacopoeia.
MOXIFLOXACIN TABLETS

Moxifloxacini compressi

Category. Antibacterial, antituberculosis.

Labelling. The designation on the container of moxifloxacin tablets should state that the active ingredient is Moxifloxacin hydrochloride and the quantity should be indicated in terms of equivalent amount of moxifloxacin.

Additional information. Strength in the current WHO Model list of essential medicines (EML) 400 mg per tablet. Strength in the current WHO EML for children: 400 mg per tablet.

Requirements. Comply with the monograph for Tablets.

Definition. Moxifloxacin tablets contain Moxifloxacin hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of moxifloxacin (C₂₁H₂₄FN₃O₄) stated on the label.

Identity tests

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R5 as the coating substance and a mixture of 4 volumes of 1-butanol R, 2 volumes of methanol R and 2 volumes of ammonia (~100 g/L) TS as the mobile phase. Apply separately to the plate 10 µL of each of the following 2 solutions: For solution (A), shake a quantity of the powdered tablets, equivalent to 20 mg of moxifloxacin with 20 mL of methanol R and filter. Dilute 1 mL of the filtrate to 20 mL with methanol. For solution (B), use a 0.055 mg/mL solution of moxifloxacin hydrochloride RS in methanol R. Develop the plate for a distance of 15 cm. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of air. Examine the chromatogram under ultraviolet light (365 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to moxifloxacin in the chromatogram obtained with solution (B).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions 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 moxifloxacin in the chromatogram obtained with solution (2).

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 hydrochloric acid (~3.65 g/L) TS and rotating the paddle at 50 revolutions per minute. At 30 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. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution, suitably diluted with the dissolution medium, if necessary, at the maximum at about 295 nm, using the dissolution medium as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of moxifloxacin hydrochloride RS in the dissolution medium.

For each of the tablets, calculate the total amount of moxifloxacin (C₂₁H₂₄FN₃O₄) in the medium. Each mg of moxifloxacin hydrochloride (C₂₁H₂₅ClFN₃O₄) is equivalent to 0.917 mg of moxifloxacin (C₂₁H₂₄FN₃O₄).
Evaluate the results as described under 5.5 Dissolution test for solid oral dosage forms, Acceptance criteria. The amount of moxifloxacin in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

[Note from the Secretariat. It is intended to determine the absorptivity value of moxifloxacin during the establishment of moxifloxacin hydrochloride RS. The value will then be included in the test description.]

Related substances. Perform the test in subdued light, preferably using low-actinic glassware. Carry out the tests as described under 1.14.4 High-performance liquid chromatography using a stainless-steel column (25 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded phenylsilyl groups (5 µm).1

Use the following mobile phase: mix 28 volumes of methanol R and 72 volumes of a solution containing 0.5 g/L of tetrabutylammonium hydrogen sulfate R, 1.0 g/L of potassium dihydrogen phosphate R and 3.4 g/L of phosphoric acid (~1440 g/L) TS.

Operate with a flow rate of 1.3 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 293 nm. Maintain the column temperature at 45 °C.

Prepare solvent (A) by dissolving 0.50 g of tetrabutylammonium hydrogen sulfate R and 1.0 g of potassium dihydrogen phosphate R in about 500 mL of water R. Add 2 mL of phosphoric acid (~1440 g/L) TS and 0.050 g of anhydrous sodium sulfite R, then dilute to 1000.0 mL with water R.

Prepare the following solutions in solvent (A). For solution (1), dissolve a quantity of the powdered tablets, equivalent to 100.0 mg of moxifloxacin in 100.0 mL of solvent (A) with sonication and filter. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 2.0 mL of this solution to 10.0 mL. For solution (3), use a solution containing 1 mg per mL of moxifloxacin for peak identification RS (containing moxifloxacin and the impurities A, B, C, D and E.

Inject alternately 10 µL of solution (1), (2) and (3). Record the chromatograms for 2.5 times the retention time of moxifloxacin.

Use the chromatogram supplied with moxifloxacin for peak identification RS and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B, C, D and E in the chromatogram obtained with solution (1). The impurities, if present, are eluted at the following relative retention with reference to moxifloxacin (retention time about 14 minutes): impurity F about 0.9; impurity A about 1.1; impurity B about 1.3; impurity C about 1.4, impurity D about 1.6 and impurity E about 1.7.

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peak due to moxifloxacin and the peak due to impurity A is at least 1.5 and the chromatogram obtained is similar to the chromatogram supplied with moxifloxacin for peak identification RS.

---

1 A Zorbax Eclipse XDB-Phenyl column was found suitable.
In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);

- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 3.5, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);

- the area of any peak corresponding to impurity A, C, D and F is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);

- the area of any other impurity peak is not greater than twice the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.2 %);

- the sum of the corrected areas of any peak corresponding to impurity B and E and the areas of all other impurity peaks is not greater than 10 times the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (1%). Disregard any peak with an area less than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%).

**Assay.** Carry out the test as described under 1.14.4 *High-performance liquid chromatography* using the conditions given under “Related substances”.

Prepare the following solutions in solvent (A). For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing the equivalent of 500.0 mg of moxifloxacin into a 500 mL volumetric flask. Add 400 mL of solvent (A), sonicate for 30 minutes, dilute to volume and filter. Dilute 1 volume of the filtrate to 10 volumes. For solution (2), use a solution containing 0.11 mg moxifloxacin hydrochloride RS per mL.

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

Measure the areas of the peaks corresponding to moxifloxacin obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of $\text{C}_{21}\text{H}_{24}\text{FN}_{3}\text{O}_{4}$ in the tablets using the declared content of $\text{C}_{21}\text{H}_{25}\text{ClFN}_{3}\text{O}_{4}$ in moxifloxacin hydrochloride RS. Each mg of $\text{C}_{21}\text{H}_{25}\text{ClFN}_{3}\text{O}_{4}$ is equivalent to 0.917 mg of moxifloxacin ($\text{C}_{21}\text{H}_{24}\text{FN}_{3}\text{O}_{4}$).

**Impurities.** The impurities limited by the requirements of this monograph include the impurities listed in the monograph for Moxifloxacin hydrochloride (excluding impurity G).
MOXIFLOXACIN HYDROCHLORIDE
(MOXIFLOXACINI HYDROCHLORIDUM)

Draft proposal for *The International Pharmacopoeia* (March 2019)

*DRAFT FOR COMMENTS*

Please send any comments you may have to Dr Herbert Schmidt, Medicines Quality Assurance Programme, Technologies, Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4856 or email: schmidt@who.int by 30 April 2019.

In order to speed up the process for receiving draft monographs and for sending comments, please send your email address to jonessi@who.int and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

*Note from the Secretariat.* The proposed monograph is based on information found in the Ph.Eur.8.0, Pharmeuropa 29.3, USP 39 and the Indian Pharmacopoeia 2014, in the scientific literature, submitted by pharmaceutical manufacturers and on laboratory investigations performed by a WHO Collaborating Centre and a collaborating laboratory.

The monograph is proposed for inclusion in *The International Pharmacopoeia*
**MOXIFLOXACIN HYDROCHLORIDE**

*Moxifloxacini hydrochloridum*

**Molecular formula.**  $C_{21}H_{25}ClFN_3O_4 \cdot H_2O$

**Relative molecular mass.**  455.9

**Graphic formula**

![Graphic formula of moxifloxacin hydrochloride](image)

**Chemical name.**  1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid monohydrochloride monohydrate (IUPAC); 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, hydrochloride, hydrate (1:1:1) (CAS); CAS Reg. No. 192927-63-2.

**Description.** A light yellow or yellow powder or crystals.

**Solubility.** Sparingly soluble in water R, slightly soluble in ethanol (~ 760 g/L) TS, practically insoluble in acetone R.

**Category.** Antibacterial, antituberculosis.

**Storage.** Moxifloxacin hydrochloride should be kept in tightly closed containers, protected from light.

**Labelling.** The designation on the container of Moxifloxacin hydrochloride should state the substance is in the form of the monohydrate.

**Additional information.** Moxifloxacin hydrochloride may exhibit polymorphism.

**Requirements**

**Definition.** Moxifloxacin hydrochloride contains not less than 98.0% and not more than 102.0% (“Assay”, method A) or not less than 99.0% and not more than 101.0% (“Assay”, method B) of $C_{21}H_{25}ClFN_3O_4$, calculated with reference to the anhydrous substance.

**Identity tests**

- Either tests A, D and E or tests B, C, D and E 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 moxifloxacin hydrochloride RS or the reference spectrum of moxifloxacin hydrochloride. If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and moxifloxacin hydrochloride RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from moxifloxacin hydrochloride RS.
B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R5 as the coating substance and a mixture of 4 volumes of 1-butanol R, 4 volumes of methanol R and 2 volumes of ammonia (~100 g/L) TS as the mobile phase. Apply separately to the plate 10 µL of each of the following 2 solutions: for solution (A), use a 0.05 mg/mL solution of the test substance in methanol R. For solution (B), use a 0.05 mg/mL solution of moxifloxacin hydrochloride RS in methanol R. Develop the plate for a distance of 15 cm. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air. Examine the chromatogram under ultraviolet light (365 nm).

The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to moxifloxacin in the chromatogram obtained with solution (B).

C. Dissolve 25 mg of the test substance in about 20 ml of methanol and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml of this solution to 100.0 ml using methanol R. The absorption spectrum (1.6) of the resulting solution, when observed between 250 and 320 nm, exhibits a maximum at about 295 nm.

D. Carry out test D.1 or test D.2.

D.1 Determine the specific optical rotation (1.4) using a solution of 0.200 g of the test substance in 20.0 mL of a mixture of equal volumes of acetonitrile R and water R and calculate with reference to the anhydrous substance $\left[\alpha\right]_{D}^{25^\circ}$ = -125 to -138.

D.2 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions and solutions given under “Impurity G (moxifloxacin enantiomer).” The retention time of the principal peak obtained with solution (1) corresponds to the retention time of the peak due to moxifloxacin in the chromatogram obtained with solution (3).

E. Dissolve 50 mg of the test substance in 5 mL of water R, add 1 mL of nitric acid (~130 g/L) TS, mix, allow to stand for 5 min and filter. The filtrate yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

Clarity and colour of solution. Dissolve 1.0 g of the test substance in 20 mL of sodium hydroxide (~85 g/L) TS. The solution is not more opalescent than opalescence standard TS3 and not more intensely coloured than reference solution GY2 (1.11.2, Method II).

pH value (1.13). pH of a 2 mg/mL solution in carbon-dioxide-free water R, 3.9 to 4.6.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using 0.200 g of the substance, 30 mL anhydrous methanol, and 3 minutes stirring before titration starts; the water content is not less than 34 mg/g and not more than 45 mg/g.

Sulfated ash (2.3). Not more than 1.0 mg/g, determined on 1.0 g in a platinum crucible.
**Impurity G (moxifloxacin enantiomer).** Perform the test in subdued light, preferably using low-actinic glassware.

Carry out the test as described under *1.14.4 High-performance liquid chromatography* using a stainless-steel column (15 cm x 3.0 mm), packed with particles of end-capped silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3 μm).²

Prepare the following chiral reagent solution. Dissolve 0.47 g of anhydrous copper (II) sulfate R and 1.31 g of isoleucine R in 1000 mL of water R and adjust with sodium hydroxide (~4 g/L) TS to a pH of 4.50.

Use the following conditions for gradient elution:

Mobile phase A: 500 volumes of methanol R and 1500 volumes of chiral reagent solution.

Mobile phase B: 225 volumes of methanol R and 450 volumes of chiral reagent solution.

<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>0–50</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>50–51</td>
<td>100 to 0</td>
<td>0 to 100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>51–61</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>61–62</td>
<td>0 to 100</td>
<td>100 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>62–85</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 0.42 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 295 nm.

Prepare the following solutions in mobile phase A. For solution (1), dissolve 200.0 mg of the test substance in 25.0 mL. For solution (2), dilute 3.0 mL of solution (1) to 200.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3), use a solution containing 0.1 mg of moxifloxacin for system suitability RS (containing moxifloxacin and impurity G) per mL.

Inject alternately 1.5 μL of solution (1), (2) and (3).

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to impurity G (with a relative retention of about 0.78 with respect to the peak due to moxifloxacin) and the peak due to moxifloxacin (retention time about 35 minutes) is at least 2.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity G (moxifloxacin enantiomer) is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.15%).

² An ACE C18 column was found suitable.
**Related substances.** Perform the test in subdued light, preferably using low-actinic glassware. Carry out the tests as described under 1.14.4 High-performance liquid chromatography using a stainless-steel column (25 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded phenylsilyl groups (5 µm).³

Use the following mobile phase: Mix 28 volumes of methanol R and 72 volumes of a solution containing 0.5 g/L of tetrabutylammonium hydrogen sulfate R, 1.0 g/L of potassium dihydrogen phosphate R and 3.4 g/L of phosphoric acid (~1440 g/L) TS.

Operate with a flow rate of 1.3 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 293 nm. Maintain the column temperature at 45 °C.

Prepare solvent (A) by dissolving 0.50 g of tetrabutylammonium hydrogen sulfate R and 1.0 g of potassium dihydrogen phosphate R in about 500 mL of water R. Add 2.0 mL of phosphoric acid (~1440 g/L) TS and 0.050 g of anhydrous sodium sulfite R, then dilute to 1000.0 mL with water R.

Prepare the following solutions in solvent (A). For solution (1), dissolve 50.0 mg of the test substance and dilute to 50.0 mL. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3), use a solution containing 1 mg per mL of moxifloxacin for peak identification RS (containing moxifloxacin and the impurities A, B, C, D and E).

Inject alternately 10 µL of solution (1), (2) and (3). Record the chromatograms for 2.5 times the retention time of moxifloxacin.

Use the chromatogram supplied with moxifloxacin for peak identification RS and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B, C, D and E in the chromatogram obtained with solution (1). The impurities, if present, are eluted at the following relative retention with reference to moxifloxacin (retention time about 14 minutes): impurity F about 0.9, impurity A about 1.1; impurity B about 1.3, impurity C about 1.4, impurity D about 1.6 and impurity E about 1.7.

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peak due to moxifloxacin and the peak due to impurity A is at least 1.5 and the chromatogram obtained is similar to the chromatogram supplied with moxifloxacin for peak identification RS.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 3.5, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity A, C, D and F is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any other impurity peak is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.10%);

³ A Inertsil Ph and a Zorbax Eclipse XDB-Phenyl column were found suitable.
• the sum of the corrected areas of any peak corresponding to impurity B and E and the areas of all other impurity peaks is not greater than 3 times the area of the peak due to moxifloxacin obtained with solution (2) (0.3 %). Disregard any peak with an area less than 0.5 times the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.05%).

**Assay**

• Either test A or test B may be applied.
  
  **A.** Carry out the test as described under *114.4 High-performance liquid chromatography* using the conditions given under “Related substances”.

  Prepare the following solutions in solvent (A). For solution (1), dissolve 50.0 mg of the test substance to be examined and dilute to 50.0 mL. Dilute 2.0 mL of this solution to 20.0 mL. For solution (2), dissolve 50.0 mg of moxifloxacin hydrochloride RS and dilute to 50.0 mL. Dilute 2.0 mL of this solution to 20.0 mL.

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

  Measure the areas of the peaks corresponding to moxifloxacin obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of C21H25ClFN3O4, using the declared content of C21H25ClFN3O4 in moxifloxacin hydrochloride RS.

  **B.** Dissolve 0.320 g of the test substance in 50 ml of water R. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Read the volume added to reach the first point of inflection. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 43.79 mg of C21H25ClFN3O4.

**Impurities**

![Chemical structure](image1)

**A.** 1-Cyclopropyl-6,8-difluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (synthesis-related impurity)

![Chemical structure](image2)

**B.** 1-Cyclopropyl-6,8-dimethoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (synthesis-related impurity)
C. 1-Cyclopropyl-8-ethoxy-6-fluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (synthesis-related impurity)

D. 1-Cyclopropyl-8-fluoro-6-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (synthesis-related impurity)

E. 1-Cyclopropyl-6-fluoro-8-hydroxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (synthesis-related impurity)

F. 1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (synthesis-related impurity)

G. 1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (moxifloxacin enantiomer) (synthesis-related impurity)
H. Methyl 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylate (synthesis-related impurity)

**Reagent to be added**

**Copper (II) sulfate R, anhydrous**

CuSO₄.

*Description.* Greenish-grey powder, hygroscopic, freely soluble in water.

*Solubility.* Slightly soluble in methanol and practically insoluble in ethanol (~750 g/L) TS.

**Isoleucine R**

(2S,3S)-2-Amino-3-methylpentanoic acid; C₆H₁₃NO₂

*Description.* White or almost white, crystalline powder or flakes.

*Solubility.* Sparingly soluble in water, slightly soluble in ethanol (~750 g/L) TS. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

**Sodium hydroxide (~85 g/L) TS**

A solution of sodium hydroxide R in water R containing about 85 g/L of NaOH.

**Sodium sulfite, anhydrous R**

Anhydrous sodium sulfite of a suitable quality should be used.

**Reference substances to be added**

Moxifloxacin hydrochloride RS.

Moxifloxacin for system suitability RS (containing moxifloxacin and impurity G).

Moxifloxacin for peak identification RS (containing moxifloxacin and the impurities A, B, E and F).
POLICY ON REMAINING SHELF LIFE
OF MEDICAL PRODUCTS

(March 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int) by 5 May 2019.

Medicines Quality Assurance working documents will be sent out electronically only. They will also be placed on the Medicines website for comment under “Current projects”. If you have not already received our draft working documents, please send your email address (to
POLICY ON REMAINING SHELF LIFE
OF MEDICAL PRODUCTS

1. INTRODUCTION

Following discussions relating to establishing policy for shelf life of medical products, including the discussion between the Interagency Pharmaceutical Coordination (IPC) group representatives, it was decided to initiate a project to have a policy on remaining shelf life for procurement and supply of medical products.

The concept and project to establish such a policy was also discussed during the meeting of the Fifty-Third Expert Committee on Specifications for Pharmaceutical Products (ECSPP) in October 2018. It was noted that some guidance documents were available from different procurement agencies. It was agreed that the World Health Organization (WHO) will initiate the discussion and preparation of a policy whilst following the WHO process for the establishment of a policy paper.

The information and policy on remaining shelf life was collected from different agencies and interested parties and a first draft document was prepared after an informal discussion meeting at the offices of The Global Fund to Fight AIDS, Tuberculosis and Malaria, in Geneva, Switzerland, in January 2019.

It was agreed that the policy should not cover only pharmaceutical products but should be extended to also cover other products, including but not limited to, diagnostics, reagents, and kits.

The draft document will be circulated to IPC members and through other channels to invite comments. The comments will be reviewed during informal discussion meetings before being tabled at the meeting of the Fifty-fourth ECSPP in October 2019.

The policy contained in this document is intended to address remaining shelf life of medical products and should be implemented by all stakeholders in the supply chain of medical products. It is also recommended that the policy be considered in the national policy of countries.

The aims of this policy document include:

- to ensure that there is a balance between enforcing the remaining shelf life policy and ensuring availability of product;
- to facilitate the national authorization of importation of stock where applicable;
- to assist in ensuring that there is sufficient stock of medical products, with acceptable remaining shelf life, in-country;
- to prevent dumping of medical products;
- to ensure that barriers to access and supply are addressed;
- to prevent stock-outs;
- to prevent receiving donations of medical products that are not appropriate; and
- to prevent having expired stock.
2. SCOPE

The principles contained in this document should be applied to medical products in the supply chain, including pharmaceutical products, medical devices, diagnostics, reagents and others.

Policy on remaining shelf life should be realistic. It should be defined for medical products and the detail may vary for different categories of products, depending on the type of product, storage condition, resources in-country and others.

This document presents policy on shelf life and does not address details contained in other guidelines, guides and agreements between different parties in the supply chain.

(Note from Secretariat: it is suggested to add references to those relating to Donations, Public Health Emergencies and Products needed in exceptional circumstances. Proposals for references are welcome).

Manufacturers, suppliers, donors and recipients should take note of the shelf life policy contained in this document.

3. THE NEED FOR POLICY

As there was no harmonized policy on shelf life for medical products amongst procurers and donors, it was agreed that it will be beneficial to have a harmonized approach on policy for shelf life. This will assist suppliers, donors, procurers and distribution points in managing medical products throughout the supply chain, ensuring the availability of quality products within the remaining shelf life, in reaching the end user.

The authorization of importation of medical products by national regulatory authorities (NRA) sometimes further delay access to medical products. A harmonized approach may facilitate authorization.

This policy document is not a standalone document. It should be read with other documents and guidelines, including but not limited to, WHO Guidelines on Stability Testing, Good Storage and Distribution Practices, Donations, Model Quality Assurance System for Procurement Agencies (MQAS), Pharmacopoeia, ICH guidelines, and other related guides and recommendations.

4. POLICY ON SHELF LIFE: MANUFACTURERS, SUPPLIERS, DONORS AND RECIPIENTS

The manufacturing date of a product should be defined by the manufacturer and be provided upon request by the recipient. This will help to ensure that an accurate shelf life can be calculated and verified.

Products, such as pharmaceutical products, should have an expiry date allocated by the manufacturer. The expiry date should be established based on stability testing results obtained in the relevant packaging (primary and secondary packaging where appropriate) and required stability conditions. (See WHO Guideline: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Technical Report Series 1010, Annex 10, 2018.)
Products with an expiry date should not be subjected to re-testing by the purchaser or recipient for the purpose of extension of shelf life.

Where a manufacturer or supplier has obtained approval from an NRA, where applicable - for a new or extended shelf life - this should be applied to batches of product to be delivered. Only in exceptional cases, such as product shortages, should a recipient consider to extend the expiry date of received batches subject to certain conditions, such as availability of scientific data. (See Annex.)

Products with a re-test date allocated by a manufacturer or supplier should have at least one year of shelf life remaining (from the date of delivery to the labelled re-test date) on the date of delivery.

Products with a re-test date allocated by a manufacturer, e.g. chemicals and reagents, may be re-tested and used if the quality parameters are met.

Products with an “Install by” date should be installed prior to the date specified by the supplier.

The principles contained in this policy document should be applied to managing donated products. (See WHO Guidelines on Donations.)

Products received should be scrutinised to be able to identify possible substandard and falsified products. It should be ensured that, for example, the expiry date is not falsified. (See Guidelines on Substandard and Falsified Products, WHO Guidance on Testing of “suspect” falsified medicines.)

Products should be appropriately labelled. The label should include the expiry, re-test or install by date, as appropriate.

Products should be transported, received, stored and distributed in accordance with Good Storage and Distribution Practices. Special attention should be given to temperature sensitive products. (Ref: WHO GSP, GDP, Temperature Sensitive materials.)

Products supplied by the manufacturer or supplier should meet the policy requirements in terms of remaining shelf life prescribed by the recipient. Compliance with this requirement should be verified by the appropriate means, such as a pre-shipment inspection.

Where different periods for remaining shelf life have been defined for products, recipients should ensure that the products meet the remaining shelf life requirement for the intended destination, e.g. central warehouse, regional warehouse or user point.

National authorization for importation, where required, should be obtained based on the available information, including the supplier specified remaining shelf life, to assist in expediting approval.

Recipients should regularly verify that products in stock are rotated or used within their remaining shelf life.

There should be an agreement between the supplier and purchaser covering the relevant responsibilities of each party and policies relating to, for example, remaining shelf life, transport conditions and returns.
The policies should be applicable to all products including emergency supplies. Where so justified, suppliers, recipients and national authorities may negotiate deviations from the remaining shelf life policy provided that:

(a) the product quality will be ensured, and

(b) where the shelf life is shorter than stipulated in the policy, it is ensured that the stock will be consumed prior to expiry of the batch.

Examples of considerations and recommended remaining shelf life of products are given in the Annexure.

**GLOSSARY**

*Note: Definitions will be taken from existing WHO guidelines where possible. Alternatively, from other recognised guidelines. In case specific definitions are required, comments will be welcomed and considered*

*Expiry date*

*Install by date*

*Manufacturing date*

*Medical product*

*Pharmaceutical product*

*Remaining shelf life*

*Re-test date*
ANNEXURE

EXAMPLES OF CONSIDERATIONS AND RECOMMENDED REMAINING SHELF LIFE OF PRODUCTS

Examples of considerations in determining the remaining shelf life:

- existing shelf life;
- required storage conditions;
- risk management;
- type of product;
- frequency of order;
- need and emergency;
- warehouse; and
- supply chain and resources.

Recommended remaining shelf life of products

Table 1. Classification depending on the expiry date

<table>
<thead>
<tr>
<th>Expiry date *</th>
<th>Remaining shelf life at time of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 5 years</td>
<td>2 years</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td>18 months</td>
</tr>
<tr>
<td>1 to 2 years</td>
<td>8 months</td>
</tr>
</tbody>
</table>

*Based on stability testing, as stipulated on the label. Presented in number of years, based on the calculation from the date of manufacture.

Table 2. Classification depending on storage conditions

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Remaining shelf life at time of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 30 °C</td>
<td>(See Table 3, unless there are opinions that the remaining shelf life should be considered purely on storage conditions)</td>
</tr>
<tr>
<td>Below 25 °C</td>
<td></td>
</tr>
<tr>
<td>2 to 8 °C</td>
<td></td>
</tr>
<tr>
<td>Below 0 °C</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Recommended remaining shelf life (alternative to Table 1 and 2)*

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Less than 2 years</th>
<th>2 – 3 years</th>
<th>3 – 4 years</th>
<th>4 – 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 0</td>
<td>8 months</td>
<td>1 year</td>
<td>1 year</td>
<td>1 year</td>
</tr>
<tr>
<td>2 to 8 °C</td>
<td>8 months</td>
<td>1 year</td>
<td>1 year</td>
<td>1 year</td>
</tr>
<tr>
<td>&lt; 25 °C</td>
<td>8 months</td>
<td>18 months</td>
<td>24 months</td>
<td>2 years</td>
</tr>
<tr>
<td>&lt; 30 °C</td>
<td>8 months</td>
<td>18 months</td>
<td>24 months</td>
<td>2 years</td>
</tr>
</tbody>
</table>

*The remaining shelf is calculated, based on expiry date, storage conditions and risks.
ENVIRONMENTAL ASPECTS OF GOOD MANUFACTURING PRACTICES:
POINTS TO CONSIDER FOR MANUFACTURERS AND INSPECTORS IN THE
PREVENTION OF ANTIMICROBIAL RESISTANCE

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Valeria Gigante (gigantev@who.int), Technical Officer, Medicines Quality Assurance, with a copy to Claire Vogel (vogelc@who.int) by 14 June 2019.

Medicines Quality Assurance working documents will be sent out electronically only. They will also be placed on the Medicines website for comment under “Current projects”. If you have not already received our draft working documents, please send your email address (to jonessi@who.int).
ENVIRONMENTAL ASPECTS OF GOOD MANUFACTURING PRACTICES:
POINTS TO CONSIDER FOR MANUFACTURERS AND INSPECTORS
IN THE PREVENTION OF ANTIMICROBIAL RESISTANCE

1. INTRODUCTION AND SCOPE

1.1. Background

Growing antimicrobial resistance (AMR) linked to the discharge of drugs and particular chemicals
into the environment is one of the most worrying health threats today, according to research by UN
Environment (1). AMR accounts for an estimated 700 000 deaths per year and, by 2030, will represent
up to US$ 3.4 trillion in Gross Domestic Product (GDP) loss (2). AMR has been identified as a
priority at the World Health Assembly since 1998 (3), with rising momentum throughout the years.
Since 1998, there have been a series of resolutions on AMR. This paved the way to the Sixty-Eighth
World Health Assembly in May 2015, where the World Health Assembly endorsed a global action
plan to tackle AMR, including antibiotic resistance, the most urgent drug resistance trend (4). More
recently, the Thirteenth General Programme of Work (2019-2023) highlighted the need to address
this emerging threat under the section for «Tackling antimicrobial resistance» (2). It is only recently
that the need to address waste and wastewater management from pharmaceutical production has been
explicitly addressed. Namely, on 30 November 2018, the World Health Organization’s (WHO)
Executive Board meeting decided that technical input will be provided to Good Manufacturing
Practice (GMP) guidance on waste and wastewater management from the production of Critically
Important Antimicrobials (5, 6). This “points to consider” document was written further to this
recent decision.

This document is to be considered as a time-limited document that addresses the current needs for
guidance on how GMPs should be implemented to waste and wastewater management for production
of antimicrobials, with a focus on Critically Important Antimicrobials. Wherever possible, this text is
informed by relevant evidence. However, the evidence base may be weak in some areas, therefore
inputs from stakeholders and experts could be beneficial.

1.2. Purpose

The purpose of this document is to:

• Raise awareness of medicines’ manufacturers, GMP inspectors and inspectorates in all
  Member States on sections of relevant GMP guidance that are applicable to the management
  of waste/wastewater from the production of antimicrobials.

• Provide clarification on the interpretation of those clauses and specific measures that should
  be taken to be considered compliant with the relevant sections of GMP guidance.

• Raise awareness of medicine’s manufacturers, GMP inspectors and inspectorates, on the
  importance of considering all aspects of GMP implementation and to also focus on the parts
  of GMP that may not have a direct product quality impact.
• Raise awareness of Member States, to establish and enforce requirements for their local pharmaceutical production facilities to safely dispose of the waste and wastewater that is generated while manufacturing antimicrobials, with a focus on Critically Important Antimicrobials.

• Provide proposals on what should be done by the different stakeholders in order to help control and reduce contamination of the environment with antimicrobials and related chemicals coming from pharmaceutical production processes.

• Discuss options and tools to reduce and mitigate the uncontrolled disposal of waste and wastewater containing antimicrobials when manufacturing medical products, with a focus on how GMP can more comprehensively address environmental aspects in the prevention of AMR, including the potential role of inspectors to tackle this issue. This includes:
  - a presentation of a pilot process in the WHO Prequalification (PQT) Inspectorate to comprise verification of adequate preventive measures in place to prevent environmental contamination with Critically Important Antimicrobials manufactured at medicines manufacturing facilities, involving both active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) production facilities;
  - a discussion of a proposal to update GMP guidelines, with a focus on the guidelines WHO good manufacturing practices for pharmaceutical products containing hazardous substances (Annex 3, TRS957, 2010) (7);
  - a discussion of the creation of a network/forum coordinated by WHO to share information, experience and mechanisms for reporting eventual potential breaches of national/international laws on waste discharge; and
  - a proposal to initiate an awareness campaign among Member States, which includes GMP inspectors.

• Gather stakeholders’ inputs on potential way forwards to tackle AMR, including successful experiences and best practices when manufacturing pharmaceutical products.

This document is not intended to cover AMR issues that are related to the clinical or veterinary setting or to other types of environmental contamination (7) (such as the excretion of antimicrobials during their use).

1.3. **Target audience**

This document is primarily targeted to:

• All manufacturers of antimicrobials who are involved in the manufacturing of API and FPPs.

• GMP inspectors and inspectorates from national medicines regulatory authorities.

• Regulatory bodies that are responsible for enforcing environmental protection standards and waste/waste water management in all Member States; consistent with a multidisciplinary approach, the Ministries of Health, Ministries of Environment or Pollution control boards and Ministries of Agriculture, as appropriate.
• Waste and wastewater management services who handle antimicrobial waste and/or process effluents from the pharmaceutical industry.

• Procurement agencies who are purchasing antimicrobials and, more particularly, Critically Important Antimicrobials, who include a verification of compliance with GMP requirements as part of their quality assurance process and/or who aim to purchase antimicrobial medicines from companies who have sustainable and environmentally respectful production processes.

• NGOs and other non-state actors who are involved in monitoring and mitigating AMR.

• Experts in environmental development and the spread of AMR, with a focus on the release of antimicrobials from manufacturing.

• Experts in waste and wastewater treatment technologies applicable in antimicrobial manufacturing.

2. GLOSSARY

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

**Antimicrobial resistance (AMR)**
Antibiotic resistance develops when bacteria adapt and grow in the presence of antibiotics. The development of resistance is linked to how often antibiotics are used. Because many antibiotics belong to the same class of medicines, resistance to one specific antibiotic agent can lead to resistance to a whole related class. Resistance that develops in one organism or location can also spread rapidly and unpredictably through, for instance, the exchange of genetic material between different bacteria and can affect antibiotic treatment of a wide range of infections and diseases. Drug-resistant bacteria can circulate in populations of human beings and animals, through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration. Resistant bacteria can be found in food, animals and food products destined for consumption by humans. Some of these features also apply to medicines that are used to treat viral, parasitic and fungal diseases, hence the broader term antimicrobial resistance.

**Active pharmaceutical ingredient (API)**
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.

**Finished pharmaceutical product (FPP)**
A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.
3. IMPACT OF API AND FPP PRODUCTION PROCESSES ON ANTIMICROBIAL-RESISTANCE

We may be entering a post-antibiotic era where simple and previously treatable bacterial infections can kill and where routine medical procedures that rely on antibiotic preventative treatment, such as joint replacements and chemotherapy, will not be possible. The 2014 O’Neill report commissioned by the Government of the United Kingdom of Great Britain and Northern Ireland estimated that antimicrobial resistant infections may become the leading cause of death globally by 2050 (1).

The environment is key to antibiotic resistance. Bacteria in soil, rivers and seawater can develop resistance through contact with resistant bacteria (transfer of resistance genes), antibiotics, disinfectant agents released by human activity (1) as well as heavy metals (8, 9) that may propagate AMR in the environment. People and livestock could then be exposed to more resistant bacteria through food, water and air (1).

The levels of pollution with antibiotics have been measured in waters in the proximity of pharmaceutical production facilities. Antimicrobial concentrations in some effluents are too low to be lethal to exposed bacteria but may still be sufficient to induce antimicrobial resistance (1, 10), but high concentrations have been found downstream of antimicrobial manufacturing sites in several countries. Scientific literature reports a correlation between the type and number of highly resistant bacteria and the level of antimicrobial pollution (10). This led to manufacturing sites being identified as hot spots for antimicrobial resistance development, but this knowledge dates from only a few years ago (11).

Poor control of waste and wastewater, such as that encountered in some of the countries who are major global producers of APIs and FPPs, can often lead to the entry of antibiotics into waters that are contaminated with pathogenic bacteria from untreated sewage. This increases the risk of the development of antimicrobial resistance. Furthermore, a vast array of contaminants in municipal and industrial wastewater increases pressure on bacteria to become resistant (1, 11).

Concentrations in river water depend on wastewater treatment facilities as well as antibiotic use in the populations they serve. Treatment plants are generally designed to remove conventional pollutants, such as nutrients, organic matter, suspended solids and pathogens, but not pharmaceuticals such as antimicrobial agents (1). Often, there is little or no treatment of manufacturing effluents or pharmaceutical waste leaving municipal wastewater treatment plants to handle the waste. However, the activated sludge may up-concentrate some antimicrobial agents, as well as antimicrobial resistant bacteria, increasing the risk for AMR in environments where the sludge is applied. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (12) that do not receive waste from antimicrobial manufacturing.

It is therefore important to significantly reduce the concentration of antimicrobials before disposal into the environment.
Action has already been initiated by some Member States, however, most of the Critically Important Antimicrobials are being manufactured in countries where legislation on environmental protection is still in its infancy and its enforcement is considered to be a challenge.

**Example box**

In the European Union (EU), there are legislative measures in place to control industrial pollution and to prevent the contamination of the water environment by listed priority substances (13). However, new measures are soon to be proposed through the new One Health action plan (14) to specifically focus on limiting antimicrobial discharges from the pharmaceutical manufacturing process in the EU.

There is an urgent call for cross-cutting pluri-sectorial action with a strong coordination and action plan coming from Ministers of Health.

Manufacturers of antimicrobials, with a special focus on API manufacturers, should implement waste stream analyses, waste management and wastewater treatment at source. Some manufacturers have launched voluntary initiatives in this regard. In 2016, a number of pharmaceutical companies presented a roadmap on combating AMR in the run-up to the United Nations General Assembly (UNGA) High-level Meeting on AMR. It committed to a list of actions, including taking action on their own manufacturing and supply chains for managing antibiotic discharge and the establishment of science-based, risk-driven targets in order to establish good practices reducing the environmental impact of manufacturing discharge by 2020 (15).

The contributions of GMP inspectors/inspectorates, procurers, NGO’s/Non-state actors are also of particular importance.

4. **REVIEW OF ENVIRONMENTAL ASPECTS OF GMP**

GMP are, a priori, intended to control the manufacture of the medicines and in principle do not focus on the environmental aspects of these. However, GMP include many aspects related to the protection of the environment and workers. If fully implemented, GMP should therefore prevent waste of all sorts appearing in the environment.

Given that the lack of control in the downstream processes of manufacturing medicines will ultimately lead to their loss in efficacy, we may no longer focus only on the aspects of GMP that are directly linked to the quality of medicines. Medicines that are no longer effective lose their value and it is therefore crucial for manufacturers and all stakeholders to take action in order to protect the efficacy of those medicines. No major new class of antibiotics have been discovered since 1987 and too few antibacterial agents are in development to meet the challenge of multidrug resistance (16).

The WHO GMP main principles for pharmaceutical products text (17) and WHO GMP for APIs (18) contain a limited set of clauses related to environmental issues. Waste and wastewater management is addressed only briefly.
On the other hand, the *WHO good manufacturing practices for pharmaceutical products containing hazardous substances (Annex 3, TRS957, 2010)* (7) contains more detailed requirements regarding waste and wastewater management which can be applied to the production of antimicrobials (see Appendix 1 for relevant clauses). These guidelines cover those hazardous substances traditionally belonging to reproductive health hormones and highly potent or sensitizing medicines such as steroids, cephalosporins and beta-lactam antibiotics. According to these guidelines, a hazardous substance or product is a *product or substance that may present a substantial risk of injury, to health or to the environment*. As antimicrobials, when released into the environment through their action on microorganisms, are deemed to present a substantial risk of injury to both health and the environment, they should be considered for inclusion in the scope of this guidance.

The guidelines require risk assessments to determine the potential hazards to the operators and to the environment of hazardous substances contained in all types of waste. Such risk assessments should therefore be performed by manufacturers as required, in principle, for any substance deemed to be hazardous.

The guidance currently requires that the external atmosphere and the public near the facility should be protected from harm from hazardous substances.

The guidance already requires neither the product or its residues of hazardous products handled in a facility should be allowed to be discharged directly to normal drainage systems.

The guidance states that if liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain. However, manufacturers seem not to have noted this, that the municipal drain may not be suitable to handle the large quantities of hazardous effluents such as those that are released by large pharmaceutical companies.

The guidance also contains the general statement that liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the personnel or to the environment.

It also states that all effluents should be disposed in a safe manner and that the means of disposal should be documented. Where external contractors are used for effluent disposal, they should have certification authorizing them to handle and treat hazardous products.

The guidance currently requires that the external atmosphere and the public near the facility should be protected from harm from hazardous substances.

The documents that the manufacturing facilities should possess are not explicit in this guidance. Manufacturers, however, would be expected to retain documentation on the following:

- Waste stream analysis for each antimicrobial agent produced, updated whenever there is a change in production affecting waste streams.

- The quantity and nature of the waste generated, including documentation of analysis performed and their findings on the hazardous substances it contains.
• Monthly reports on its collection, treatment and disposal.

• Information on the methods used to treat the waste – they should be documented to be effective for each specific hazardous substance contaminant. Analytical data demonstrating the conversion of hazardous substances and their residues to non-hazardous waste materials should be available at the facility and kept up to date.

• If effective waste treatment is not yet implemented for all waste streams concerning each API or FPP, documentation on a time-limited strategy should be in place with specified milestones for that implementation. This documentation should be maintained at the facility regardless of whether or not an external contractor has been used.

5. PROPOSALS FOR STAKEHOLDERS

5.1. Manufacturers of medicines

FPP and API manufacturers should thoroughly examine their waste and waste management processes to ensure that antimicrobial residues are treated in a safe and effective manner. The industry could take a role in developing standards for pharmaceutical waste containing antimicrobials.

5.2. National GMP inspectorates from all Member States

The following actions are proposed:

• Implementation of WHO guidelines on hazardous substances or equivalent GMP guidelines to the production of antimicrobials.

• Train inspectors on inspection of waste and wastewater management processes and instruct inspectors to include inspection of those aspects for all sites who are manufacturing Critically Important Antimicrobials during routine GMP inspections.

• Increase the level of communication between the GMP inspectorates and their local national regulatory bodies who are responsible for enforcing environmental protection standards.

5.3. Regulatory bodies responsible for enforcing environmental protection from pharmaceutical waste

In all Member States, consideration should be given to developing national action plans for AMR and for strengthening the legislation for waste and wastewater management and its enforcement. Inspectors within the relevant departments (e.g. Ministries of Health, Ministries of Environment or Pollution Control Boards) of waste/wastewater treatment plants should be trained on aspects relating to decontamination of antimicrobials.
Programs for sampling and testing of wastewater and effluents should be implemented to monitor compliance with local/international regulation and with the effectiveness of the decontamination and mitigation strategies.

5.4. **Procurers of antimicrobial medicines**

Procurement agencies who purchase antimicrobials, particularly Critically Important Antimicrobials, are encouraged to purchase those medicines from companies who have sustainable and environmentally respectful production processes.

6. **PROPOSAL FOR WHO’S OPTIONS AND TOOLS USING WHO GMP**

While focusing on how WHO can more comprehensively address environmental aspects for the prevention of AMR and the potential contributing role of inspectors to tackling this issue, WHO has the following options and tools to reduce and mitigate the uncontrolled disposal of waste and wastewater containing antimicrobials when manufacturing medical products.

6.1 **Pilot process in the WHO PQT Inspectorate**

A pilot process will be initiated by 2020 by WHO’s Prequalification Team Inspectorate (19) to include verification of adequate measures to prevent environmental contamination with antimicrobials. It will focus on Critically Important Antimicrobials manufactured at both APIs and FPPs’ medicines manufacturing facilities. The *WHO good manufacturing practices for pharmaceutical products containing hazardous substances (Annex 3, TRS957, 2010)* will continue to be enforced during inspections with an increased level of scrutiny for Critically Important Antimicrobials. Deficiencies should be noted in case of non-compliances.

Adequate corrective and preventive actions will be verified for those deficiencies and will be a condition for making a conclusion on the level of GMP compliance of manufacturing sites.

After each successful facility inspection close-out, a WHO Public Inspection Report is published (20). To provide greater transparency and to enable the verification of adequate compliance with requirements by stakeholders, consideration should be given to including a section in the WHO Public Inspection Reports on waste and wastewater management. This would provide a means for procurers to make informed decisions, taking into consideration the environmental impact of the medicines they purchase.

Approximately one year after its launch, the effectiveness of this pilot process will be monitored to decide whether or not it should be modified, strengthened or expanded.
6.2 Proposal to update GMP guidelines

The following modifications to the guidelines *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (Annex 3, TRS957, 2010) should be considered:

- To enable a thorough and effective verification of compliance and to avoid the use of external contractors as a loophole, manufacturing facilities should be specifically required to possess adequate documentation. This should include:
  - documentation of waste stream analysis for each API or FPP;
  - the quantity and nature of the waste generated, including analytical information on the hazardous substances it contains;
  - monthly reports on its collection, treatment and disposal;
  - for facilities with already implemented waste treatment, information on the methods used to treat the waste – they should be documented to be effective for each specific hazardous substance contaminant. Analytical data demonstrating the conversion of hazardous substances and their residues to non-hazardous waste materials should be available at the facility and kept up to date; and
  - for facilities without waste treatment of all waste streams, a time limited strategy should be in place, specifying actions towards achieving treatment that significantly reduces the concentration of the API (and its microbial source, when relevant) or FPP.

This documentation should be maintained at the facility regardless of whether or not the facility treats its own waste or discharges it to an external contractor or third-party waste water treatment plant, with or without pretreatment (e.g. pH adjustment, chelation, precipitation, etc.).

- The guidance currently requires that the external atmosphere and the public in the vicinity of the facility should be protected from harm from hazardous substances. In the proposed revision, the inclusion of effluents and water streams should be considered in this section because the literature contains several reports of effluents close to facilities being contaminated with dangerous levels of antimicrobials.

- Including guidance on acceptable methods of decontamination of manufacturing waste containing antimicrobials and on mitigation strategies. Many decontamination methods already exist that reduce or remove antibiotics (and microbes that have produced fermentative antimicrobials) from waste streams entering the environment from antimicrobial manufacturing: secondary and tertiary waste water treatment; membrane filtration and ozonation; and UV disinfection and heat treatment, which are even more effective at removing viable bacteria (*I, II*). Incineration may also be considered for solid or semi-liquid waste. The level of effectiveness and by-products should be considered when adopting a particular approach.
6.3 Creation of a network/forum coordinated by WHO

Currently, there are no established mechanisms to share information, know-how, mechanisms or instruments to report an eventual breach of national/international laws on waste discharge. Establishing a multi-disciplinary network of experts and regulators would be key to improving the sharing of information between inspectorates and the relevant departments of Member States so that appropriate action is taken in a timely manner in the event of any breaches. Procedures should be established for communication between WHO, GMP inspectorates and all relevant regulators from Member States, independent technical experts and research groups on AMR.

6.4 Awareness campaign among Member States

WHO has launched awareness campaigns on antimicrobial resistance in several regions. However, there have not yet been any campaigns specifically targeted at the production of antimicrobials and towards waste and wastewater management. This should be considered for inclusion in future campaigns. GMP inspectorates, regulatory bodies that are responsible for enforcing environmental protection standards and waste/wastewater management such as Ministries of Health, Ministries of Environment or Pollution Control Boards and Ministries of Agriculture should also be targeted by those campaigns.

REFERENCES


5. Follow-up to the high-level meetings of the United Nations General Assembly on health-related issues - Antimicrobial resistance - Report by the Director-General, Executive Board Meeting, 144th session, Agenda item 5.8, EB144/19, 30 November 2018. http://apps.who.int/gb/ebwha/pdf_files/EB144/B144_19-en.pdf


11. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Yong-Guan Zhu et al., 2013. Environ Health Perspect, 121(8)).


19. WHO Essential Medicines and Health Products Prequalification of Medicines. Inspections. https://extranet.who.int/prequal/content/inspections-0

20. WHO Public Inspection Reports (WHOPIRS). https://extranet.who.int/prequal/key-resources/prequalification-reports/whopirs

ACRONYMS

AMR: antimicrobial resistance
API: active pharmaceutical ingredient
ARB: antibiotic resistant bacteria
ARG: antimicrobial resistance gene
FPP: finished pharmaceutical product
GMP: good manufacturing practices
UNGA: United Nations General Assembly
APPENDIX 1

Relevant sections of WHO guidelines and proposals for modification

A. ANNEX 3, TRS 957, 2010. GUIDANCE ON WHO GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES

2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows: — to ensure quality of product; — to protect the operators from possible harmful effects of products containing hazardous substances; and — to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.

7. Environmental protection

7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.
(Note from Secretariat: effluents or water streams should also be considered.)

7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.
(Note from Secretariat: the municipal drain may not be suitable to handle large quantities of hazardous effluents and therefore manufacturers are requested to consider this in their approach.)
13. Effluent treatment

13.1 Liquid and solid waste effluent should be handled in such a manner so as not to present a risk of contamination to the product, personnel or to the environment.

13.2 All effluent should be disposed of in a safe manner and the means of disposal should be documented. Where external contractors are used for effluent disposal, they should have certification authorizing them to handle and treat hazardous products.

(Note from Secretariat: manufacturers should possess adequate and detailed documentation on those aspects.)

B. ANNEX 2, TRS957, 2010. WHO GOOD MANUFACTURING PRACTICES FOR ACTIVE PHARMACEUTICAL INGREDIENTS

4.6 Sewage and refuse

Sewage, refuse and other waste (e.g. solids, liquids or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

C. ANNEX 2, TRS986, 2014. WHO GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS: MAIN PRINCIPLES

14.4 Waste materials

14.44 Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.