DISSOLUTION TEST FOR SOLID ORAL DOSAGE FORMS

Draft proposal for revision in *The International Pharmacopoeia*

**DRAFT FOR COMMENTS**

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by 31 August 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonesi@who.int and your name will be added to our electronic mailing list.

**[Note from the Secretariat. Chapter 5.5 Dissolution test for solid oral dosage form is based on the internationally-harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It is proposed to add to the chapter a section for the analysis of Suspensions and powders for suspension, which did not undergo harmonization and is not part of the PDG text. Comments are sought on the new section.**

Changes from the current text are indicated in the text by insert or delete.]
Revision of chapter 5.5 DISSOLUTION TEST FOR SOLID ORAL DOSAGE FORMS

5.5 DISSOLUTION TEST FOR SOLID ORAL DOSAGE FORMS

This text is based on the internationally-harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It has been developed in line with the style and requirements used in the International Pharmacopoeia. The additional sections on Suspensions and powders for oral suspension and on monographs of the International Pharmacopoeia are not part of the PDG text.

For further guidance, see also the chapter Dissolution testing of tablets and capsules in the Supplementary Information section.

This test determines the amount of active ingredient(s) released from a solid oral dosage form, such as a tablet or a capsule, under controlled conditions using a known volume of dissolution medium within a predetermined length of time.

Basket apparatus. The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material, which should not sorb, react or interfere with the preparation to be tested; a motor; a drive shaft; and a cylindrical basket (stirring element). The vessel is partially immersed in a suitable water-bath of any convenient size or heated by a suitable device such as a heating jacket. The water-bath or heating device permits maintaining the temperature inside the vessel at 37 ± 0.5 ºC during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation or vibration beyond that due to the smoothly rotating stirring element. An apparatus that permits observation of the preparation and stirring element during the test is preferable. The vessel is cylindrical with a hemispherical bottom and a capacity of 1 litre. Its height is 160–210 mm and its inside diameter is 98–106 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of samples. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at a specified rate within ± 4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. A basket having a gold coating of about 2.5 µm (0.0001 inch) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.
1. Screen with welded seam: 0.22–0.31 mm wire diameter with wire opening of 0.36–0.44 mm. After welding, the screen may be slightly altered.

2. Maximum allowable runout at “A” is 1.0 mm when the part is rotated on centre line axis with basket mounted.

*Figure 1. Basket stirring element*

Dimensions in millimetres.
A and B dimensions do not vary more than 0.5 mm when part is rotated on centre line axis. Tolerances are ± 1.0 mm unless otherwise stated.

Figure 2. Paddle stirring element

Dimensions in millimetres.
**Paddle apparatus.** Use the assembly from the basket apparatus except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical centre line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of $25 \pm 2$ mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of non-reactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 3. Other validated sinker devices may be used.

*Figure 3. Alternative sinker. A: acid-resistant wire clasp; B: acid-resistant wire support; Dimensions in millimeters.*
Recommended procedure

Conventional-release (or immediate-release) dosage forms

Procedure. Place the stated volume of the dissolution medium (± 1%) in the vessel of the specified apparatus. Assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5 °C and remove the thermometer. The test may also be carried out with the thermometer in place, provided it is shown that results equivalent to those obtained without the thermometer are obtained. Place one dosage unit in the apparatus taking care to exclude air bubbles from the surface of the dosage unit. Operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw a sample from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade not less than 1 cm from the vessel wall. Agitation/stirring should continue during sampling. Where multiple sampling times are specified replace the samples withdrawn for analysis with equal volumes of fresh dissolution medium at 37 °C or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test and verify the temperature (37 ± 0.5 °C) of the medium at suitable times. Perform the analysis as directed in the individual monograph using a suitable assay method. The samples are filtered immediately upon sampling, preferably by using in-line filtration or a filter in the tip of the sampling probe or both, unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis. Centrifugation is not recommended unless validated for the specific test. The test is to be conducted with six dosage form units in parallel.

If automated equipment is used for sampling or the apparatus is otherwise modified verification is necessary that the modified apparatus will produce results equivalent to those obtained with the apparatus described in this chapter.

Dissolution medium. A suitable dissolution medium is used. The volume specified refers to measurements made between 20 °C and 25 °C. If the dissolution medium is a buffered solution adjust the solution so that its pH is within 0.05 units of the specified pH. Dissolved gases can cause bubbles to form which may change the results of the test. In such cases, dissolved gases must be removed prior to testing.1

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1 One appropriate method of deaeration is as follows: heat the medium, while stirring gently, to about 41 °C, immediately filter under vacuum using a filter having a pore size of 0.45 µm or less, with vigorous stirring and continue stirring under vacuum for at least 5 minutes, preferably 15 minutes, until no more bubbles are observed. Other validated deaeration techniques for removal of dissolved gases may be used.
**Time.** Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Samples are to be withdrawn only at the stated times, within a tolerance of ± 2%.

Determine the quantity of active ingredient dissolved at the specified time(s) indicated in the individual monograph. The result should be expressed as a percentage of the content stated on the label of the dosage form.

**Sustained-release (or extended-/prolonged-release) solid-dosage forms**

**Procedure.** Proceed as described for conventional-release dosage forms.

**Dissolution medium.** Proceed as described for conventional-release dosage forms.

**Time.** The test-time points, generally three, are expressed in hours.

**Delayed-release solid-dosage forms**

**Procedure.** Use method A or B.

**Method A**

- **Acid stage.** Place 750 mL hydrochloric acid (0.1 mol/L) VS in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in hydrochloric acid (0.1 mol/L) VS, withdraw a sample of the fluid and proceed immediately as directed under buffer stage. Perform an analysis of the sample using a suitable assay method.

- **Buffer stage.** Complete the operations of adding and adjusting the pH within 5 minutes. With the apparatus operating at the rate specified, add to the fluid in the vessel 250 mL of a 0.2 M solution of trisodium orthophosphate R that has been equilibrated to 37 ± 0.5 °C. Adjust, if necessary, with hydrochloric acid (~70 g) TS or sodium hydroxide (~80 g/L) TS to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes or for the specified time. At the end of the time period, withdraw a sample of the fluid and perform the analysis using a suitable assay method.
Method B

- **Acid Stage.** Place 1000 mL of hydrochloric acid (0.1 mol/L) VS in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in hydrochloric acid (0.1 mol/L) VS, withdraw a sample of the fluid and proceed immediately as directed under buffer stage. Perform an analysis of the sample using a suitable assay method.

- **Buffer stage.** For this stage of the procedure, use buffer that has previously been equilibrated to a temperature of 37 ± 0.5 °C. Drain the acid from the vessel and add 1000 mL of pH 6.8 phosphate buffer, prepared by mixing three volumes of hydrochloric acid (0.1 mol/L) VS with one volume of a 0.20 M solution of trisodium orthophosphate R and adjusting, if necessary, with hydrochloric acid (~70 g/L) TS or sodium hydroxide (~80 g/L) TS to a pH of 6.8 ± 0.05. This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer. Continue to operate the apparatus for 45 minutes or for the specified time. At the end of the time period, withdraw a sample of the fluid and perform the analysis using a suitable assay method.

*Time.* All test times stated are to be observed within a tolerance of ± 2%, unless otherwise specified.

**Acceptance criteria**

*Conventional-release (or immediate-release) dosage forms*

Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 1. Continue testing through the three levels unless the results conform at either S1 or S2. The quantity, Q, is the specified amount of dissolved active ingredient expressed as a percentage of the labelled content; the 5%, 15% and 25% values in the acceptance table are percentages of the labelled content so that these values and Q are in the same terms.
Table 1

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>6</td>
<td>Each value is not less than $Q + 5%$.</td>
</tr>
<tr>
<td>$S_2$</td>
<td>6</td>
<td>Average value of the 12 dosage units ($S_1 + S_2$) is equal to or greater than $Q$ and no unit is less than $Q - 15%$.</td>
</tr>
<tr>
<td>$S_3$</td>
<td>12</td>
<td>Average value of 24 dosage units ($S_1 + S_2 + S_3$) is equal to or greater than $Q$; not more than 2 units are less than $Q - 15%$; no unit is less than $Q - 25%$.</td>
</tr>
</tbody>
</table>

Sustained-release (or extended-/prolonged-release) dosage forms

Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 2. Continue testing through the three levels unless the results conform at either $L_1$ or $L_2$. Limits on the amounts of active ingredient(s) dissolved are expressed in terms of the labelled content. The limits embrace each value of $Q$, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified, the acceptance criteria apply individually to each range.

Table 2

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_1$</td>
<td>6</td>
<td>No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.</td>
</tr>
<tr>
<td>$L_2$</td>
<td>6</td>
<td>The average value of the 12 dosage units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of the labelled content outside each of the stated ranges; and none is more than 10% of labelled content below the stated amount at the final test time.</td>
</tr>
<tr>
<td>$L_3$</td>
<td>12</td>
<td>The average value of the 24 dosage units ($L_1 + L_2 + L_3$) lies within the stated ranges and is not less than the stated amount at the final test time; not more than 2 of the 24 dosage units are more than 10% of labelled content outside each of the stated ranges; not more than 2 of the 24 dosage units are more than 10% of labelled content below the stated amount at the final test time; and none is more than 20% of labelled content outside each of the stated ranges or more than 20% of labelled content below the stated amount at the final test time.</td>
</tr>
</tbody>
</table>
Delayed-release dosage forms

*Acid stage.* Unless otherwise stated in the individual monograph, the requirements of this part of the test are met if the quantities, based on the percentage of the labelled content of active ingredient(s) dissolved from the dosage units tested conform to Table 3. Continue testing through the three levels unless the results of both acid and buffer stages conform at an earlier level.

**Table 3**

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>6</td>
<td>No individual value exceeds 10% dissolved.</td>
</tr>
<tr>
<td>A₂</td>
<td>6</td>
<td>Average value of the 12 dosage units ((A₁ + A₂)) is not more than 10% dissolved, and no individual value is greater than 25% dissolved.</td>
</tr>
<tr>
<td>A₃</td>
<td>12</td>
<td>Average value of 24 dosage units ((A₁ + A₂ + A₃)) is not more than 10% dissolved, and no individual value is greater than 25% dissolved.</td>
</tr>
</tbody>
</table>

*Buffer stage.* Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredients dissolved from the units tested conform to Table 4. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in Table 4 is 75% dissolved unless otherwise specified. The quantity, Q, is the specified total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a percentage of the labelled content. The 5%, 15% and 25% values in the table are percentages of the labelled content so that these values and Q are in the same terms.

**Table 4**

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₁</td>
<td>6</td>
<td>No value is less than (Q + 5%).</td>
</tr>
<tr>
<td>B₂</td>
<td>6</td>
<td>Average value of the 12 dosage units ((B₁ + B₂)) is equal to or greater than (Q), and no unit is less than (Q - 15%).</td>
</tr>
<tr>
<td>B₃</td>
<td>12</td>
<td>Average value of the 24 dosage units ((B₁ + B₂ + B₃)) is equal to or greater than (Q); not more than 2 units are less than (Q - 15%), and no unit is less than (Q - 25%).</td>
</tr>
</tbody>
</table>
Suspensions and Powders for oral suspension

Procedure. Prepare a suspension from Powders for oral suspension or re-suspend suspensions according to the product information. Avoid the introducing of bubbles into the sample to ensure the precision of dosing. Transfer to the dissolution apparatus, preferably by weight, the amount of sample indicated in the monograph. If no amount is given, use an amount that is equivalent to 1 unit dose or, in case the product has different doses depending on body weight or age, the amount of sample that corresponds to the highest unit dose to be administered at one time. If the product is labeled for single use, each sample should come from a different container/packet.

Monographs of The International Pharmacopoeia

The following additional statements apply to the individual monographs of The International Pharmacopoeia.

Qualification of dissolution test equipment and verification of system performance

Periodically qualify the equipment utilizing an “enhanced mechanical calibration”, such as the procedure described in the international standard procedure ASTM 2503 or a combination of a mechanical calibration to determine conformance of the dissolution apparatus to the dimensions and tolerances as given above and the analysis of suitable reference tablets to verify the performance of the testing system.

Test conditions

The following specifications are given in the individual monographs:

- the apparatus to be used;
- the composition and volume of the dissolution medium;
- the rotation speed of the paddle or basket;
- the preparation of the test and reference solutions;
- the time, the method and the amount of sample to be withdrawn or the conditions for continuous monitoring; the preparation of the sample and the reference solution;
- the method of analysis; and
- the limits of the quantity or quantities of active pharmaceutical ingredient(s) required to dissolve within a prescribed time.

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Dissolution media

If a buffer is added to the dissolution medium, adjust its pH to within ± 0.05 units of the prescribed value.

In specific cases, and subject to approval by the relevant regional or national authority, dissolution media may contain enzymes and/or surfactants. The addition of enzymes may be considered, for example, for formulations containing gelatin when dissolution failures can be ascribed to the cross-linking of this excipient (e.g. hard and soft gelatin capsules; gelatin containing tablets). For the testing of preparations containing poorly aqueous-soluble active substances, modification of the medium may be necessary. A surfactant may be added only when the active pharmaceutical ingredient is insoluble over the entire physiological pH range, pH 1.2 to 6.8. In such circumstances, a low concentration of surfactant may be prescribed.

Below are some examples of dissolution media:

- **Dissolution buffer pH 1.2, TS**
  
  Dissolve 2 g of *sodium chloride* R in 800 mL of *water* R, adjust the pH to 1.2 with *hydrochloric acid* (~70 g/L) TS and dilute to 1000 mL with *water* R.

- **Dissolution buffer pH 2.5, TS**
  
  Dissolve 2 g of *sodium chloride* R in 800 mL of *water* R, adjust the pH to 2.5 with *hydrochloric acid* (~70 g/L) TS and dilute to 1000 mL with *water* R.

- **Dissolution buffer pH 3.5, TS**
  
  Dissolve 7.507 g of *glycine* R and 5.844 g of *sodium chloride* R in 800 mL of *water* R, adjust the pH to 3.5 with *hydrochloric acid* (~70 g/L) TS and dilute to 1000 mL with *water* R.

- **Dissolution buffer pH 4.5, TS1**
  
  Dissolve 2.99 g of *sodium acetate* R in 900 mL of *water* R, adjust the pH to 4.5 by adding about 14 mL of acetic acid (~120 g/L) TS and dilute to 1000 mL with *water* R.

- **Dissolution buffer pH 4.5, TS2**
  
  Dissolve 6.8 g of *potassium dihydrogen phosphate* R in 900 mL of *water* R, adjust the pH to 4.5 either with *hydrochloric acid* (~70 g/L) TS or *sodium hydroxide* (~80 g/L) TS and dilute to 1000 mL with *water* R.
• **Dissolution buffer, pH 6.8, TS**

Dissolve 6.9 g of *sodium dihydrogen phosphate* R and 0.9 g of *sodium hydroxide* R in 800 mL of *water* R, adjust the pH to 6.8 with *sodium hydroxide (~80g/L)* TS and dilute to 1000 mL with *water* R.

• **Dissolution buffer, pH 6.8, 0.25% SDS TS**

Dissolve 6.9 g of *sodium dihydrogen phosphate* R, 0.9 g of *sodium hydroxide* R and 2.5 g of *sodium dodecyl sulfate* R in 800 mL of *water* R, adjust the pH to 6.8 with *sodium hydroxide (~80g/L)* TS and dilute to 1000 mL with *water* R.

• **Dissolution buffer pH 7.2, TS**

Dissolve 9.075 g of *potassium dihydrogen phosphate* R in *water* R to produce 1000 mL (solution A). Dissolve 11.87 g of *disodium hydrogen phosphate* R in sufficient *water* R to produce 1000 mL (solution B). Mix 300 mL of solution A with 700 mL of solution B.

• **Gastric fluid, simulated, TS**

Dissolve 2.0 g of *sodium chloride* R and 3.2 g of *pepsin* R in 7.0 mL of *hydrochloric acid (~420 g/L)* VS and sufficient *water* R to produce 1000 mL. This test solution has a pH of about 1.2.

• **Intestinal fluid pH 6.8, simulated, TS**

Mix 77.0 mL of *sodium hydroxide (0.2 mol/L)* VS, 250.0 mL of a solution containing 6.8 g *potassium dihydrogen phosphate* R and 500 mL of *water* R. Add 10.0 g *pancreatin* R, mix and adjust the pH with the buffer components to 6.8 ± 0.1. Dilute to 1000 mL with *water* R.

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WHO Biowaiver Project - Preparation for cycle IV (2021):
Prioritization exercise of active pharmaceutical ingredients on the
WHO Model List of Essential Medicines for solubility determination
and Biopharmaceutics Classification System-based classification

DRAFT FOR COMMENTS

Please send your comments to Dr Valeria Gigante, Technical Officer, Norms and Standards
for Pharmaceuticals, Technical Standards and Specifications (gigantev@who.int), with a copy
to Ms Claire Vogel (vogelc@who.int) before 20 August 2020. Please use our attached
Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO
Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for
comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to
jonessi@who.int and your name will be added to our electronic mailing list.
WHO Biowaiver Project - Preparation for cycle IV (2021):
Prioritization exercise of active pharmaceutical ingredients on the
WHO Model List of Essential Medicines for solubility determination
and Biopharmaceutics Classification System-based classification

1. Introduction and scope

In October 2019, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparation (ECSPP) took note of the results achieved within the WHO Biowaiver Project and recommended continuing the Biopharmaceutics Classification System (BCS)-based classification of active pharmaceutical ingredients (APIs) contained in medicines listed in the WHO List of Essential Medicines (EML) (1) and prioritized according to public health priorities, Member States’ and WHO partners’ needs (2).

This document is intended to support the prioritization exercise of APIs that will be characterized in their solubility profile in cycle IV of the WHO Biowaiver Project, to take place in 2021 according to the ECSPP decision (2).

The WHO Biowaiver Project is organized into study cycles. Previous and current cycles are summarized below in order to provide an overview of the project development:
• 2018: cycle I; also referred to as the pilot phase.
• 2019: cycle II.
• 2020: cycle III; current study cycle.
• 2021: cycle IV. Note: this prioritization exercise is propaedeutic to this study cycle.

2. Background

When evaluating multisource (generic) products, the goal is to ensure that they have a comparable bioavailability (BA) with respect to their originator in order to assume comparability in their efficacy and safety profiles.

The WHO recognizes the possibility to waive in vivo bioequivalence studies for immediate-release, solid oral dosage forms APIs belonging to classes I and III according to the BCS, using comparative dissolution studies as surrogate proof of bioequivalence (3).

The aim of WHO biowaiver guidance documents is to reduce the risk of “bioinequivalence” to an acceptable level when granting biowaivers supporting pharmaceutical development and access to medicines. In this context, the solubility, the release from the drug product and the
subsequent absorption phase are considered critical processes underlying the equivalence of the test and reference product.

Equilibrium solubility profiles of APIs contained in medicines in the EML (1) can be used in conjunction with absorption/permeability data, finished pharmaceutical products (FPP) dissolution studies and comparative consideration of FPP-Excipient content in order to provide an informed decision on whether or not a biowaiver could be granted safely.

3. The revised WHO Biowaiver List

According to the recommendations from the Fifty-second, Fifty-third and Fifty-fourth ECSPP, the WHO Secretariat has published the revised WHO Biowaiver List: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (4). The List is published in form of a living document and is meant to be regularly updated with new data and in accordance with the scientific and technical progress in this area. In addition, the List replaces the existing literature-based compilation published in 2006 that is reported in the Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (5).

The WHO Protocol to conduct equilibrium solubility experiments for the purpose of biopharmaceutics classification system-based classification of active pharmaceutical ingredients for biowaiver (6) is a tool available to all participants in this research. This protocol was developed with the purpose of providing a harmonized methodology for the equilibrium solubility experiments, thereby minimizing the variability amongst centres and studies.

4. Prioritization exercise of active pharmaceutical ingredients for Biopharmaceutical Classification System-based classification in WHO Biowaiver Project

A fourth set of APIs is proposed for BCS-based classification within the WHO Biowaiver Project. The criteria underpinning the APIs prioritization are as follows:

- the API must be contained in medicines listed in the EML;
- the API must be intended to be formulated as an immediate-release, solid oral dosage form;
- the API must belong to therapeutic areas of major public interest; and
- the specific physical-chemical properties for the API must be known.

Consideration should be given to narrow therapeutic index drugs (NTIs) as the BCS-based biowaiver approach is not considered to be a suitable surrogate for the establishment of bioequivalence of NTIs.
COVID-19 emergency use

During this prioritization exercise, propaedeutic to the study of the solubility profiles of APIs, particular attention has been made of potential candidates currently in clinical trials to address the COVID-19 pandemic. In addition great efforts are being made to conduct an expedite characterization to address this public health emergency. Dexamethasone followed by hydroxychloroquine are therefore suggested as high priority APIs for the solubility characterization.

Note: the inclusion of these substance in the list does not imply any endorsement from WHO but is intended only to promote access to medicines in case they will be deemed suitable for the intended purpose.

Proposed list of active pharmaceutical ingredients for study in cycle IV

The list of APIs to be prioritized for BCS-based classification in the next cycle of the project (cycle IV- 2021) are proposed below (in alphabetic order) and comments are invited. When providing comments, you might wish to indicate their order of priority.

<table>
<thead>
<tr>
<th>N</th>
<th>API contained in medicines on the EML</th>
<th>Therapeutic Area</th>
<th>Indication</th>
<th>Highest therapeutic single dose [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abacavir</td>
<td>Antiretrovirals</td>
<td>Treatment and prevention of HIV</td>
<td>600 mg</td>
</tr>
<tr>
<td>2</td>
<td>Dexamethasone</td>
<td>(1) Gastrointestinal medicines/ (2) Immunomodulators and antineoplastics/ (3) Medicines for other common symptoms in palliative care</td>
<td>(1) Antiemetic medicines/ (2) Acute lymphoblastic leukaemia (2) Multiple myeloma/ (3) Medicines for other common symptoms in palliative care</td>
<td>(1) (3) 0.75 to 9 mg a day depending on the disease being treated/ (2) 40 mg</td>
</tr>
<tr>
<td>3</td>
<td>Doxycycline</td>
<td>(1) Antiprotozoals (2) Antibacterials</td>
<td>(1) Antimalarial medicines (2) Antibiotics (access group)</td>
<td>(1) and (2) 100 mg (as hyclate)</td>
</tr>
<tr>
<td>4</td>
<td>Ethambutol</td>
<td>Antibacterials</td>
<td>Antituberculosis medicines</td>
<td>2 g</td>
</tr>
<tr>
<td>5</td>
<td>Isoniazid</td>
<td>Antibacterials</td>
<td>Antituberculosis medicines</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>Medication</td>
<td>Category</td>
<td>Indication</td>
<td>Dosage</td>
</tr>
<tr>
<td>---</td>
<td>---------------------</td>
<td>---------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>6</td>
<td>Hydroxychloroquine</td>
<td>Medicines for diseases of joints</td>
<td>Disease-modifying agents used in rheumatoid disorders (DMARDs)</td>
<td>400 to 600 mg</td>
</tr>
<tr>
<td>7</td>
<td>Lamivudine</td>
<td>Antiretrovirals</td>
<td>Treatment and prevention of HIV</td>
<td>300 mg</td>
</tr>
<tr>
<td>8</td>
<td>Levonorgestrel</td>
<td>Medicines for reproductive health and perinatal care</td>
<td>Oral hormonal contraceptives</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>9</td>
<td>Nifurtimox</td>
<td>Antiprotozoal medicines</td>
<td>African trypanosomiasis and American trypanosomias</td>
<td>10.0 mg/kg</td>
</tr>
<tr>
<td>10</td>
<td>Proguanil</td>
<td>Antiprotozoals</td>
<td>Antimalarial</td>
<td>100 mg (as hydrochloride)</td>
</tr>
</tbody>
</table>

**Note:** For exemption from an in vivo bioequivalence study, an immediate release, multisource product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to the reference product. The excipients used in the formulation must be considered together with a risk-based approach in terms of the therapeutic index and clinical indications.
5. References


6. Further reading


ZANAMIVIR

(ZANAMIVIRUM)

Draft proposal for inclusion for The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (email: schmidt@who.int) by 14 September 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. It is proposed to include the monograph on Zanamivir in The International Pharmacopoeia. The monograph is based on a submission by a manufacturer and on laboratory investigations.]
ZANAMIVIR (ZANAMIVIRUM)

**Molecular formula.** $C_{12}H_{20}N_4O_7,xH_2O$

**Relative molecular mass.** 332.3 (anhydrous substance).

**Graphic formula.**

![Graphic formula of Zanamivir]

**Chemical name.** $(2R,3R,4S)-3$-Acetamido-4-carbamimidamido-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-$2H$-pyran-6-carboxylic acid hydrate; CAS Reg. No. 551942-41-7.

**Description.** A white, or almost white, slightly hygroscopic powder.

**Solubility.** Slightly soluble in water $R$, practically insoluble in ethanol (~750 g/L) TS and dichloromethane $R$.

**Category.** Antiviral.

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

**Labelling.** The designation on the container should state that the substance is in the form of the hydrate.

**Additional information.** Zanamivir may exhibit polymorphism.
Requirements

Definition. Zanamivir contains not less than 97.0% and not more than 102.0% of C_{12}H_{20}N_{4}O_{7}, calculated with reference to the anhydrous and solvent-free substance.

Identity tests

- Either test A or test B may be applied.

A. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from zanamivir RS or with the reference spectrum of zanamivir. If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and zanamivir RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from zanamivir RS.

B. Carry out test B.1 or, where a diode array detector is available, test B.2.

B.1 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 zanamivir in the chromatogram obtained with solution (2). The absorption spectrum (1.6) of a 6 µg per mL solution of the test substance in phosphate buffer, pH 7.4, TS, when observed between 200 nm and 400 nm, exhibits a maximum at 260 nm.

B.2 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. Record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and UV spectrum of the peak due to zanamivir in the chromatogram obtained with solution (2).
Specific optical rotation (1.4). Dissolve 0.250 g in 25.0 mL of water R; sonicate until the substance is dissolved. Calculate with reference to the anhydrous and solvent-free substance; the specific optical rotation is between +36.0 to +38.5.

Sulfated ash (2.3). Not more than 1.0 mg/g, determined on 1.0 g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A. The water content is not less than 40 mg/g and not more than 90 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 5; determine the heavy metals content according to Method B; not more than 20 μg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of cross-linked polyvinyl alcohol polymer with chemically bonded polyamine (5 µm).3

As the mobile phase, use a mixture of 60 volumes of acetonitrile R and 40 volumes of a 0.7 g/L solution of sulfuric acid (~1760 g/L) TS previously adjusted to pH 5.5 with ammonia (~1.7 g/L) TS.

Operate with a flow rate of 1.5 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 234 nm and, for impurity I, at 210 nm. For identity test B.2, use a diode array detector in the range of 200 nm to 400 nm. Maintain the column temperature at 30 °C. Prior to first use, rinse the column with a 0.7 g/L solution of ammonium sulfate R at 1.5 mL per minute at 30 °C for about 1 hour. Prior to each use, rinse with the mobile phase for at least 8 hours.

3 An Asahipak NH2P-50 column has been found suitable.
Prepare the following solutions. For solution (1), dissolve 23.0 mg of the test substance in 20 mL of water R and dilute to 50.0 mL with acetonitrile R[0.46 mg Z/mL]. For solution (2), dilute 1.0 mL of test solution (1) to 100.0 mL with mobile phase. Dilute 1.0 mL or this solution to 10.0 mL with mobile phase[0.1%]. For solution (3), dissolve 5 mg of zanamivir for system suitability RS (containing zanamivir and the impurities A, B, C and E) in 6 mL of water R and dilute to 10 mL with acetonitrile R. For solution (4), dissolve 3.00 mg of zanamivir impurity F RS in mobile phase and dilute to 100.0 mL with mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase. Dilute 3.0 mL of this solution to 20.0 mL with mobile phase[0.045 µg imp F/mL]. For solution (5), dissolve 10 mg of imidazole R in 40 mL of water R and dilute to 100 mL with acetonitrile R. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase.

Inject alternately 20 µL of solutions (1), (2), (3), (4) and (5) and record the chromatogram for 3 times the retention time of zanamivir.

Use the chromatogram obtained with solution (3) to identify the peaks due to the impurities A, B, C and E. Use the chromatogram obtained with solution (4) to identify the peak due to impurity F. Use the chromatogram obtained with solution (5) to identify the peak due to impurity I.

The impurities are eluted, if present, at the following relative retention with reference to zanamivir (retention time about 9 minutes): impurity I about 0.26; impurity F about 0.30; impurity B about 0.60; impurity D about 0.71; impurity C about 0.77; impurity E about 0.83; impurity H 1.14; and impurity A about 2.75.

The test is not valid unless, in the chromatogram obtained with solution (3), the peak-to-valley ratio (Hp/Hv) is at least 2.5, where Hp is the height above the baseline of the peak due to impurity E, and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C. Also, the test is not valid unless, in the chromatogram obtained with solution (4), the peak due to impurity F is obtained with a signal-to-noise ratio of at least 10.

Measure the areas of the peaks corresponding to the impurities in the chromatograms obtained with solutions (1) and (4) and the area of zanamivir in the chromatogram obtained with solution (2).
Determine the percentage content of impurity F, considering the concentration of impurity F in solution (4) and the declared content of impurity F in zanamivir impurity F RS.

- The percentage content of impurity F is not greater than 0.01%.

For impurities other than impurity F, compare the peak areas of the impurities with the peak areas of zanamivir obtained with solution (2).

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 5 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity B is not greater than 3 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.3 %);
- the area of any peaks corresponding to impurity E, when multiplied with a correction factor of 0.63, is not greater than 2 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %);
- the areas of any peaks corresponding to impurity C or D is not greater than 2 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %);
- the area of any peak corresponding to impurity I, recorded at 210 nm, when multiplied by a correction factor of 0.4, is not greater than the area of the peak due to zanamivir in the chromatogram obtained with solution (2), recorded at 210 nm (0.1 %);
- the area of any other impurity peak is not greater than the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.10 %).

Determine the sum of the areas of all impurity peaks recorded at 234 nm, other than any peak corresponding to impurity I and including the corrected area of any peak corresponding to impurity E. Disregard all peaks with an area of less than 0.5 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.05%). Calculate the percentage concentration of these impurities using the area of any peak corresponding to zanamivir in the chromatogram obtained with solution (2) as a reference. Calculate the percentage concentration of impurity I using the area of any peak corresponding to zanamivir in the chromatogram obtained with solution (2) and recorded at 210 nm as a reference. Add the percentage concentration of impurity I to the percentage concentration of all other impurities. Disregard impurity I if the percentage concentration is less than 0.05%. The percentage concentration of all impurities is not greater than 1.2%.
**Assay.** Carry out the test as described under *1.14.4 High-performance liquid chromatography*, using the conditions given above under "Related substances" with the following modifications.

Prepare the following solutions. For solution (1), dissolve 23.0 mg of the test substance in 20 mL of water R and dilute to 50.0 mL with acetonitrile R. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase. For solution (2), dissolve 23.0 mg of zanamivir RS in 20 mL of water R and dilute to 50.0 mL with acetonitrile R. Dilute 5.0 mL of this solution to 50.0 mL with mobile phase.

Inject alternately 20 µL of solutions (1) and (2) and record the chromatogram for 3 times the retention time of zanamivir.

Measure the areas of the peaks corresponding to zanamivir obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of C₁₂H₂₀N₄O₇ in the sample using the declared content of C₁₂H₂₀N₄O₇ in zanamivir RS.

**Impurities**

A. (2R,3R,4S)-3-acetamido-2-[(1R,2R)-3-[[[(2R,3R,4S)-3-acetamido-6-carboxy-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-4-yl]carbamoyl]oxy]-1,2-dihydroxypropyl]-4-carbamimidamido-3,4-dihydro-2H-pyran-6-carboxylic acid (zanamivir dimer)(synthesis-related impurity).
B. 5-Acetamido-9-O-[4-amino-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-2,6-anhydro-3,4,5-trideoxy-4-guanidino-d-glycero-d-galacto-non-2-enonic acid (O-triazinyl zanamivir) (synthesis-related impurity).

C. (2R,3R,4S)-3-acetamido-4-amino-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid (4-amino zanamivir) (synthesis-related impurity).

D. (2R,3R,4S)-3-acetamido-4-(carbamoylamino)-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid (zanamivir urea analog) (synthesis-related impurity).
E. (2R,3R,4S)-3-acetamido-4-(N-carbamimidoylcarbamimidamido)-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid (4-biguanide zanamivir) (synthesis-related impurity).

F. 1H-pyrazole-1-carboximidamide (synthesis-related impurity).

H. (2R,3R,4R)-3-acetamido-4-carbamimidamido-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid (talo-zanamivir) (synthesis-related impurity).

I. imidazole (synthesis-related impurity).
Reference substances to be established

Zanamivir for system suitability RS (containing zanamivir and the impurities A, B, C and E)
- It is intended to refer to the corresponding reference substance established by the European Pharmacopoeia.

Zanamivir impurity F
- It is intended to refer to the corresponding reference substance established by the European Pharmacopoeia.

Zanamivir RS
- International Chemical Reference Substance to be established.

Reagents to be established

Ammonia (~1.7 g/L) TS

Ammonia (~17 g/L) TS, diluted to contain about 1.7 g of NH₃ per litre (approximately 0.1 mol/L).
ZANAMIVIR POWDER FOR INHALATION, PRE-METERED
(ZANAMIVIRI PULVIS PRO INHALATIONE)

Draft proposal for inclusion for The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (email: schmidt@who.int) by 14 September 2020.

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If you wish to receive our draft guidelines, please send your e-mail address to jonest@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat: It is proposed to include the monograph on Zanamivir powder for inhalation, pre-metered in The International Pharmacopoeia. The monograph is based on a submission by a manufacturer and on laboratory investigations. It was developed in collaboration with the British Pharmacopoeia.]
ZANAMIVIR POWDER FOR INHALATION, PRE-METERED
(ZANAMIVIRI PULVIS PRO INHALATIONE)

Category. Antiviral, neuraminidase inhibitor.

Labelling. The designation of the container should indicate that the active ingredient is Zanamivir. The quantity of active ingredient is stated in terms of the equivalent amount of zanamivir per pre-metered unit.

Additional information. Zanamivir inhalation powder is listed on the third invitation to manufacturers of influenza-specific antiviral medicines to submit an Expression of Interest (EOI) for product evaluation to the WHO Prequalification Team: medicines.

Labelling. The label states the content of active ingredient per pre-metered unit.

Manufacture. The fine-particle characteristics of the aerosol cloud generated by the powder for inhalation is controlled so that a consistent portion is deposited in the lung. The test and limits for the aerodynamic assessment of the fine particles (fine particle dose) should be agreed with the relevant regulatory authority.

Requirements
Complies with the monograph on Powders for Inhalation.

Definition. Zanamivir powder for inhalation, pre-metered consists of Zanamivir, in the form of microfine powder or equivalent, either alone or combined with a suitable carrier. The pre-metered unit is loaded into a dry-powder inhaler to generate an aerosol. It contains not less than 90.0% and not more than 110.0% of the amount of C12H20N4O7 per pre-metered unit as stated on the label.
Identity tests

A. Transfer a quantity of the powder, nominally containing 10 mg of Zanamivir, into a 50 mL flask, add 50 mL of a mixture of 1 volume of formamide R and 2 volumes of methanol R and sonicate for five minutes to dissolve excipients. Filter the suspension and dry the residue at 120 °C for about one hour. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from zanamivir RS similarly treated.

B. Carry out test B.1 or, where a diode array detector is available, test B.2.
   B.1 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 zanamivir in the chromatogram obtained with solution (2).
   The absorption spectrum (1.6) of a solution of the powder in phosphate buffer, pH 7.5, TS, nominally containing 6 µg of Zanamivir per mL, when observed between 200 nm and 400 nm, exhibits a maximum at 260 nm.

B.2 Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. Record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and UV spectrum of the peak due to zanamivir in the chromatogram obtained with solution (2).

Uniformity of delivered dose. Complies with the test for Uniformity of delivered dose stated under Powders for Inhalation using the following method of analysis.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under “Assay”, with the following modifications.

Prepare as a diluent a mixture of 60 volumes of acetonitrile R and 40 volumes of water R. Prepare the following solutions. For solution (1), dissolve the collected dose in sufficient diluent to produce a solution, nominally containing 0.05 mg of Zanamivir per mL. For solution (2), use solution (2) as described under “Assay”.

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

Calculate the content of C\textsubscript{12}H\textsubscript{20}N\textsubscript{4}O\textsubscript{7} in each delivered dose using the declared content of C\textsubscript{12}H\textsubscript{20}N\textsubscript{4}O\textsubscript{7} in zanamivir RS.

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under “Assay”, with the following modifications:

Prepare the following solutions. For solution (1), transfer a quantity of the powder, nominally containing 20 mg of Zanamivir, into a 50.0 ml volumetric flask. Add about 45 mL of mobile phase and sonicate for five minutes.[BP: 10 mg Z in 25 ml]. Allow to cool to room temperatures and make up to volume with mobile phase[0.4 mg Z/mL]. For solution (2), dilute 1.0 mL of solution (1) to 200.0 mL with mobile phase[0.5%]. For solution (3), dissolve 5 mg of zanamivir for system suitability RS (containing zanamivir and the impurities A, B, C and E) in mobile phase and dilute to 10 mL with the same solvent. For solution (4), dissolve 2.67 mg of zanamivir impurity F RS in mobile phase and dilute to 100.0 mL with mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase. Dilute 3.0 mL of this solution to 20.0 mL with mobile phase[0.04 µg imp F/mL]. For solution (5), dilute 1.0 mL of solution (2) to 200.0 mL with mobile phase [0.1%].

Inject alternately 10 [20 ul in the API monograph. GSK advises to inject 10 ul]µL of solutions (1), (2), (3), (4) and (5) and record the chromatogram for 3[4 times BP] times the retention time of zanamivir.

Use the chromatogram obtained with solution (3) and the chromatogram supplied with zanamivir for system suitability to identify the peaks due to the impurities A, B, C and E. Use the chromatogram obtained with solution (4) to identify the peak due to impurity F. The impurities are eluted, if present, at the following relative retention with reference to zanamivir (retention time about 9 minutes): impurity F about 0.30; impurity B about 0.60; impurity D about 0.71; impurity C about 0.77; impurity E about 0.83; impurity H about 1.14; impurity A about 2.75[RR from GSK doc Zanamivir API test methods for WHO].
The test is not valid unless, in the chromatogram obtained with solution (3), the peak-to-valley ratio \((H_p/H_v)\) is at least 2.5, where \(H_p\) is the height above the baseline of the peak due to impurity E and \(H_v\) is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity C. Also, the test is not valid unless in the chromatogram obtained with solution (5) the peak due to impurity F is obtained with a signal-to-noise ratio of at least 10.

Measure the areas of the peaks corresponding to the impurities of zanamivir in the chromatograms obtained with solution (1) and (4) and the area of zanamivir in the chromatogram obtained with solution (2).

Determine the percentage content of impurity F, considering the concentration of the impurity in solution (4) and the declared content of impurity F in zanamivir impurity F RS.

- The percentage content of impurity F is not greater than 0.01%.

For impurities other than impurity F, compare the peak areas of the impurities with the peak areas of zanamivir obtained with solution (2).

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity B is not greater than 0.6 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.3 %);
- the area of any peaks corresponding to impurities C or D is not greater than 0.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 0.63, is not greater than 0.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (0.2 %).
- The sum of the areas of all impurity peaks, including the corrected area of any peak corresponding to impurity E, is not greater than 2.4 times the area of the peak due to zanamivir in the chromatogram obtained with solution (2) (1.2%). Disregard all peaks with an area or less than the area of the peak due to zanamivir 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 a stainless steel column (25 cm x 4.6 mm) packed with cross-linked polyvinyl alcohol polymer with chemically bonded polyamine (5 µm)⁴. As the mobile phase use a mixture of 60 volumes of acetonitrile R and 40 volumes of a 0.7 g/L solution of sulfuric acid (~1760 g/L) TS previously adjusted to pH 5.5 with ammonia (~1.7 g/L) TS.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 234 nm. For identity test B.2 use a diode array detector in the range of 200 nm to 400 nm. Maintain the column temperature at 30 °C. Prepare as a diluent a mixture of 60 volumes of acetonitrile R and 40 volumes of water R. Prepare the following solutions. For solution (1), weigh and powder the contents of 24 pre-metered units. Transfer a quantity of the mixed contents, nominally equivalent to 50.0 mg of Zanamivir to a 100 mL volumetric flask. Add about 90 mL of water R and sonicate for 5 minutes. Allow to cool to room temperature and make up to volume with water R. Dilute 10.0 mL of this solution to 100.0 mL with diluent. For solution (2), dissolve 50.0 mg of zanamivir RS in diluent and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with diluent.

Inject alternately 10 µL each of solution (1) and (2). Record the chromatogram for 3 times the retention time of zanamivir.

Measure the areas of the peaks corresponding to zanamivir obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of C₁₂H₂₀N₄O₇ per pre-metered unit using the declared content of C₁₂H₂₀N₄O₇ in zanamivir RS.

⁴ An Asahipak NH2P-50 column has been found suitable.
Impurities
The impurities limited by the requirements of this monograph include those listed in the monograph on Zanamivir.

Reference substances to be established
Zanamivir for peak identification RS (containing zanamivir and the impurities A, B, C and E)
- It is intended to refer to the corresponding reference substance established for the European Pharmacopoeia.

Zanamivir impurity F
- It is intended to refer to the corresponding reference substance established by the European Pharmacopoeia.

Zanamivir RS
- ICRS to be established.

Reagent to be established
Ammonia (~1.7 g/L) TS

Ammonia (~17 g/L) TS, diluted to contain about 1.7 g of NH₃ per litre (approximately 0.1 mol/L).

***
POWDERS FOR INHALATION  
(PULVIS AD INHALATIONEM)  
Draft proposal for inclusion in The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by 14 September 2020.

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If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. It is proposed to include a general monograph on Powders for inhalation in The International Pharmacopoeia. The text was drafted based on the corresponding texts in the chapter Preparations for inhalation of the European Pharmacopoeia (Ph.Eur.) and the Japanese Pharmacopoeia (JP), which underwent bilateral harmonization between these pharmacopoeias. During the course of development, the text has undergone changes.]
POWDERs FOR INHALATION
(INHALANDA)

This text was drafted based on the corresponding texts in the chapters on Preparation of inhalation of the European Pharmacopoeia and the Japanese Pharmacopoeia. During the course of development, the text has undergone changes.

**Definition**

Powders for inhalation are solid preparations intended to be converted to aerosols and orally administered to the lung using a breath-actuated inhaler.

Powders for inhalation may be supplied in single-dose containers for use in pre-metered inhalers or in multidose containers for use in either pre-metered or device-metered powder inhalers. Pre-metered inhalers are loaded with powders pre-dispersed in capsules or other suitable dosage forms. Device-metered inhalers may use a powder reservoir where the dose is created by a metering mechanism within the inhaler.

Powders for inhalation contain one or more active pharmaceutical ingredients. To facilitate the use of powders for inhalation, the active pharmaceutical ingredients may be combined with suitable excipients, e.g. a carrier substance. These excipients do not adversely affect the functions of the mucosa of the respiratory tract or its cilia.

**Additional information**

The delivered dose is the dose delivered from the inhaler. For some preparations, the labelled dose has been established as a metered dose or as a pre-metered dose. The metered dose is determined by adding the amount deposited on the inhaler to the delivered dose. It may also be determined directly.

**Manufacture**

The manufacturing processes for powders for inhalation should meet the requirements of good manufacturing practices (GMP).

The fine-particle characteristics of the aerosol cloud generated by the powder for inhalation is controlled so that a consistent portion is deposited in the lung.

During the development of a powder for inhalation that contains an antimicrobial preservative, the effectiveness of the chosen preservative shall be demonstrated to the satisfaction of the relevant regulatory authority.
In the manufacture, packaging, storage and distribution of powders for inhalation, suitable measures are taken to ensure their microbial quality. Recommendations on this aspect are provided in the chapter titled *Microbiological quality of non-sterile products: recommended acceptance criteria for pharmaceutical preparations* in the supplementary information section. For a multidose powder inhaler, uniformity of a delivered dose must be ensured within a device (intra-inhaler) and between devices (inter-inhaler). For intra-inhaler testing, the uniformity of delivered dose tests are described below. For inter-inhaler testing, an example of a suitable procedure is to take 10 inhalers and collect a single dose from each inhaler, collecting the dose at the beginning (from 3 inhalers), middle (from 4 inhalers) and end (from 3 inhalers) of the number of doses stated on the label. Other inter-inhaler testing procedures are possible, where justified and authorized.

**Uniformity of delivered dose**

Powders for inhalation comply with the following test.

The test is carried out using a dose collection apparatus that must be capable of quantitatively capturing the delivered dose. A suitable dose collection apparatus is specified in Figure 1 and Table 1.

*Figure 1. Apparatus suitable for measuring the uniformity of delivered dose for powder inhalers*
Table 1. Specifications of the apparatus used for powder inhalers described in Figure 1.

<table>
<thead>
<tr>
<th>Code</th>
<th>Item</th>
<th>Description</th>
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<tr>
<td>A</td>
<td>Sample collection tube</td>
<td>Capable of quantitatively capturing the delivered dose, e.g. dose collection tube with dimensions of 34.85 mm ID x 12 cm length (e.g. product number XX40 047 00, Millipore Corporation, Bedford, MA 01732, USA, with modified exit tube, ID ≥ 8 mm, fitted with Gelman product number 61631), or equivalent.</td>
</tr>
<tr>
<td>B</td>
<td>Filter</td>
<td>47 mm filter, e.g. A/E glass fibre filter (Gelman Sciences, Ann Arbor, MI 48106, USA), or equivalent.</td>
</tr>
<tr>
<td>C</td>
<td>Connector</td>
<td>ID ≥ 8 mm, e.g., short metal coupling, with low-diameter branch to P3.</td>
</tr>
<tr>
<td>D</td>
<td>Vacuum tubing</td>
<td>A length of suitable tubing having an ID ≥ 8 mm and an internal volume of 25 ± 5 mL.</td>
</tr>
<tr>
<td>E</td>
<td>2-way solenoid valve</td>
<td>A 2-way, 2-port solenoid valve having a minimum airflow resistance orifice with ID ≥ 8 mm and an opening time ≤ 100 ms (e.g. type 256-A08, Bürkert GmbH, 74653 Ingelfingen, Deutschland), or equivalent.</td>
</tr>
<tr>
<td>F</td>
<td>Vacuum pump</td>
<td>Pump must be capable of drawing the required flow rate through the assembled apparatus with the powder inhaler in the mouthpiece adapter (e.g. product type 1023, 1423 or 2565, Gast Manufacturing Inc., Benton Harbor, MI 49022, USA), or equivalent. Connect the pump to the 2-way solenoid valve using short and/or wide (≥ 10 mm ID) vacuum tubing and connectors to minimize pump capacity requirements.</td>
</tr>
<tr>
<td>G</td>
<td>Timer</td>
<td>Timer capable of driving the 2-way solenoid valve for the required time period (e.g. type G814, RS Components International, Corby, NN17 9RS, UK), or equivalent.</td>
</tr>
<tr>
<td>P1</td>
<td>Pressure tap</td>
<td>2.2 mm ID, 3.1 mm OD, flush with internal surface of the sample collection tube, centred and burr-free, 59 mm from its inlet. The pressure tap P1 must never be open to the atmosphere. Differential pressure to atmosphere is measured at P1.</td>
</tr>
<tr>
<td>P2</td>
<td>Pressure measurements</td>
<td>Absolute pressures.</td>
</tr>
<tr>
<td>P3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Flow control valve</td>
<td>Adjustable regulating valve with maximum Cv ≥ 1 (e.g. type 8FV12LNSS, Parker Hannifin plc., Barnstaple, EX31 1NP, UK), or equivalent.</td>
</tr>
</tbody>
</table>
Unless otherwise stated, determine the test flow rate and duration using the dose collection tube, the associated flow system, a suitable differential pressure meter and a suitable volumetric flowmeter, calibrated for the flow leaving the meter, according to the following procedure.

Prepare the inhaler for use as directed in the instructions to the patient and connect it to the inlet of the apparatus using a mouthpiece adapter to ensure an airtight seal. Use a mouthpiece adapter that ensures that the front face of the inhaler mouthpiece is flush with the front face of the sample collection tube. Connect one port of a differential pressure meter to the pressure reading point P1 in Figure 1, and let the other be open to the atmosphere. Switch on the pump, open the 2-way solenoid valve and adjust the flow control valve until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H₂O) as indicated by the differential pressure meter. Remove the inhaler from the mouthpiece adapter and, without touching the flow control valve, connect a flowmeter to the inlet of the sampling apparatus. Use a flowmeter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter ($Q_{out}$) using the ideal gas law. For a meter calibrated for the entering volumetric flow ($Q_{in}$), use the following expression:

$$Q_{out} = \frac{Q_{in} \times P_0}{P_0 - \Delta P}$$

$P_0$ = atmospheric pressure;
$\Delta P$ = pressure drop over the meter.

If the flow rate is above 100 L/min, adjust the flow control valve to obtain a flow rate of 100 L/min (± 5 %). Note the volumetric airflow rate exiting the meter and define this as the test flow rate, $Q_{out}$, in litres per minute. Define the test flow duration, $T$, in seconds so that a volume of 4 L of air is drawn from the mouthpiece of the inhaler at the test flow rate, $Q_{out}$. Ensure that critical flow occurs in the flow control valve by the following procedure: with the inhaler in place and the test flow rate $Q_{out}$, measure the absolute pressure on both sides of the control valve (pressure reading points P2 and P3 in Figure 1); a ratio $P3/P2$ of less than or equal to 0.5 indicates critical flow; switch to a more powerful pump and re-measure the test flow rate if critical flow is not indicated.

Pre-metered inhalers. Connect the inhaler to the apparatus using an adapter that ensures a good seal. Draw air through the inhaler using the predetermined conditions. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance. Repeat the procedure for a further 9 doses.
Device-metered inhalers. Connect the inhaler to the apparatus using an adapter that ensures a good seal. Draw air through the inhaler under the predetermined conditions. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance. Repeat the procedure for a further 2 doses.

Discharge the inhaler to waste until \((n/2) + 1\) deliveries remain, where \(n\) is the number of deliveries stated on the label. If necessary, store the inhaler to discharge electrostatic charges. Collect 4 doses using the procedure described above.

Discharge the inhaler to waste until 3 doses remain. If necessary, store the inhaler to discharge electrostatic charges. Collect 3 doses using the procedure described above. For preparations containing more than 1 active substance, carry out the test for uniformity of delivered dose for each active substance.

Requirements. The preparation complies with the test if 9 out of 10 results lie between 75 % and 125 % of the mean value and all lie between 65 % and 135 %. If 2 or 3 values lie outside the limits of 75 % to 125 %, repeat the test for 2 more inhalers. Not more than 3 of the 30 values lie outside the limits of 75 % to 125 % and no value lies outside the limits of 65 % to 135 %.

In justified and authorized cases, these ranges may be extended but no value should be greater than 150 % or less than 50 % of the mean value. Unless otherwise authorized, the mean value must be between 85 % and 115 % of the label claim for delivered dose.

Fine particle dose
Using a suitable and authorized method, calculate the fine particle dose.

Number of deliveries per inhaler for multidose inhalers (this test may be combined with the test for Uniformity of delivered dose).

Using the method described in the test for Uniformity of delivered dose above, discharge doses from the inhaler until empty, at the predetermined flow rate. Record the deliveries discharged.

Requirements. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label.
Labelling
Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

The label should include:
(1) the name of the pharmaceutical product;
(2) the name(s) of the active ingredients; International Nonproprietary Names (INNs) should be used wherever possible;
(3) the amount of active ingredient in the delivered dose or, if justified and authorized (e.g. where the dose has been established as a metered dose or as a pre-metered dose), the metered dose or the pre-metered dose;
(4) where applicable, the number of deliveries from the inhaler to provide the minimum recommended dose;
(5) the number of deliveries per inhaler
(6) the name and concentration of any antimicrobial preservative and the name of any other excipient;
(7) the batch (lot) number assigned by the manufacturer;
(8) the expiry date and, when required, the date of manufacture;
(9) any special storage conditions or handling precautions that may be necessary;
(10) directions for use, warnings, and precautions that may be necessary; and
(11) the name and address of the manufacturer or the person responsible for placing the product on the market.

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GOOD MANUFACTURING PRACTICES: WATER FOR PHARMACEUTICAL USE

DRAFT FOR COMMENTS

Please send your comments to **Dr Sabine Kopp**, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before **11 September 2020**. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Background

Water quality, including microbiological and chemical quality, throughout production, storage and distribution processes, should be controlled. Unlike other product and process ingredients, water is usually drawn from an on-demand system and is not subject to testing and batch or lot release prior to use. The assurance of water quality to meet the on-demand expectation is, therefore, essential.

In recent years, following extensive consultations with stakeholders, several pharmacopoeias have adopted revised monographs on water for injection (WFI) that allow for production by non-distillation technologies. In 2017, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat collect feedback on whether or not they should revise the WHO specifications and good manufacturing practices (GMP) on WFI, and how to do so. Following discussions during several consultations, the ECSPP agreed that the monograph in The International Pharmacopoeia (Water for injections) and the guideline WHO Good manufacturing practices: water for pharmaceutical use (1), should both be revised to allow for technologies other than distillation for the production of WFI. In early 2019, the WHO Secretariat commissioned the preparation of a draft guidance text for the production of WFI by means other than distillation. Following several public consultations, the text was presented to the Fifty-fourth ECSPP. The Expert Committee adopted the Production of water for injection by means other than distillation guideline and recommended that it should also be integrated into WHO’s existing guideline on Good manufacturing practices: water for pharmaceutical use.

1. **Introduction and scope**

1.1 This document concerns water for pharmaceutical use (WPU) produced, stored and distributed in bulk form. It provides information on different specifications for WPU; good practices for quality management of water systems; water treatment (production) systems; water storage and distribution systems; commissioning, qualification and validation; sampling and testing; and the routine monitoring of water.

1.2 The focus of this document is on the treatment, storage and distribution of treated water used in pharmaceutical applications. It excludes the production, storage and usage of water in quality control laboratories.

1.3 This document does not cover water for administration to patients in the formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.

1.4 The document can be used in whole or in part, as appropriate, to the section and application under consideration.

1.5 In addition to this document, the “Further reading” section at the end of this document includes some relevant publications that can serve as additional background material when planning, installing and operating systems intended to provide WPU.

1.6 This document is supplementary to the *World Health Organization (WHO) Good manufacturing practices for active pharmaceutical ingredients (2)*, and the *WHO Good manufacturing practices for pharmaceutical products: main principles (3)*.
2. **Background to water requirements and uses**

2.1 Water is a widely used substance in the pharmaceutical industry and other establishments involved in manufacturing pharmaceutical products. It is extensively used as a raw material or starting material in the production, processing and formulation of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP), in the preparation of solvents and reagents, and for cleaning (e.g. washing and rinsing). Water has unique chemical properties due to its polarity and hydrogen bonds. These include a relatively high boiling point, high specific heat, cohesion, adhesion and density. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health. Water should therefore meet the required quality standards to mitigate these risks.

2.2 The microbiological and chemical quality of water should be controlled throughout production, storage and distribution. Water is not usually subjected to testing and batch or lot release before use. It is usually drawn from a system on-demand for use. While chemical test results can normally be obtained without delay, results from microbiological testing are normally available only after water has already been used as microbiological tests may require periods of incubation. The assurance of quality to meet the on-demand expectation of water is therefore essential.

2.3 To reduce the risks associated with the production, storage and distribution of water, and considering the properties and use, it is essential:
- to ensure the appropriate design, installation, operation and maintenance of WPU, pre-treatment, treatment, storage and distribution systems;
- to continuously or periodically perform sanitization;
- to take the appropriate measures in order to prevent chemical and microbial contamination; and
- to prevent microbial proliferation and endotoxin formation, where applicable.

2.4 Different grades of water quality exist. The appropriate water quality, meeting its defined specification (such as described in a pharmacopoeia), should be used for the intended application.

2.5 The application of specific types of water to processes and dosage forms should be considered.
2.6 Pharmaceutical manufacturers should use the appropriate grade of WPU during, for example, the manufacture of APIs and different dosage forms, for different stages in washing and cleaning, and in the synthesis of materials and products.

2.7 The grade of water used should take into account the nature and intended use of the intermediate or FPP and the stage in the manufacturing process at which the water is used.

2.8 Bulk water for injections (BWFI) should be used, for example, in the manufacture of injectable products, such as dissolving or diluting substances or preparations during the manufacturing of parenteral products, and for the manufacture of water for preparation of injections. BWFI should also be used for the final rinse after the cleaning of equipment and components that come into contact with injectable products, as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

3. **General principles for pharmaceutical water systems**

3.1 Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified, validated, operated and maintained to ensure the consistent and reliable production of water of intended quality.

3.2 The capacity of these systems should be appropriate to meet the average and peak flow demand. These systems should be able to operate continuously for significant periods of time in order to avoid the inefficiencies and equipment stresses that occur when equipment cycles turn on and off too frequently.

3.3 Following an initial qualification such as installation qualification (IQ), operational qualification (OQ), performance qualification (PQ) and validation, the release and use of the system should be approved by the quality unit, e.g. quality assurance (QA).

3.4 Water sources and treated water should be monitored regularly for chemical, microbiological and, where appropriate, endotoxin contamination. The performance of water treatment, storage and distribution systems should also be monitored. Records of the results monitored, trend analysis and any actions taken should be maintained.
4. Water quality specifications

4.1 Pharmcacepoeial specifications

4.1.1 Pharmacopoeias include specifications for water used in bulk and in dosage forms. Where this document refers to specifications, such as those in pharmacopoeias, the relevant, current publications should be used. This document does not attempt to duplicate such material. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer should choose the appropriate specification in accordance with the related marketing authorization submitted to the relevant medicine’s regulatory authority. Pharmacopoeial requirements or guidance for WPU are described in national, regional and international pharmacopoeias (4) and limits for various impurities, or classes of impurities, are either specified or recommended. Requirements or guidance are given in pharmacopoeias on the microbiological and chemical quality of water.

4.2 Drinking-water

*Note: The requirements for the design, construction and commissioning of drinking water systems are usually controlled through local regulations. Drinking water systems are not usually qualified or validated.*

4.2.1 The quality of drinking-water is covered by the *WHO guidelines for drinking-water quality* (5) and standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

4.2.2 Drinking-water may be derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water should be considered when choosing a treatment to produce drinking-water.

4.2.3 Drinking-water should be supplied under continuous positive pressure by a plumbing system free from any defects that could lead to the contamination of any product.

4.2.4 Drinking-water may be derived from a public water supply system. This includes an off-site source, such as a municipality. The appropriate drinking-water quality should be ensured by the supplier. Tests should be conducted to guarantee that the drinking-water delivered is of drinking quality. This testing is typically performed on water from the water source. Where required, the quality may be achieved through the appropriate processing on-site.

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5 See documents listed under Further reading
4.2.5 Where drinking-water is purchased in bulk and transported to the user by water tanker, controls should be put into place to mitigate any risks associated therewith. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a way similar to that used for any other starting material.

4.2.6 It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the purified water (PW) treatment system meets the appropriate drinking-water requirements. In these situations, the point at which drinking-water quality is achieved should be identified and a water sample taken and tested at defined intervals thereafter.

4.2.7 If drinking-water is used directly in certain stages of pharmaceutical manufacture, such as in the production of APIs or in the feedwater for the production of higher qualities of WPU, then testing should be carried out periodically by the water user’s site; for example, at the point of use, to confirm that the quality meets the standards required for drinking-water. The selection of tests to be performed, and the frequency of testing, should be based on risk assessment.

4.2.8 Where drinking-water is produced through the treatment of raw water by a system on-site, the system configuration and water-treatment steps used should be described.

4.2.9 Examples of typical processes employed to produce drinking-water may include:
- desalination;
- filtration;
- softening;
- disinfection or sanitization (e.g. by sodium hypochlorite (chlorine));
- iron (ferrous) removal;
- precipitation; and
- the reduction of concentration of specific inorganic and/or organic materials.

4.2.10 Controls should be implemented to prevent the microbiological contamination of sand filters, carbon beds and water softeners. The techniques selected should be appropriate and may include backflushing, chemical and/or thermal sanitization and frequent regeneration.

4.2.11 The quality of drinking-water should be monitored routinely to account for environmental, seasonal or supply changes which may have an impact on the source water quality.
4.2.12 Where drinking-water is stored and distributed by the user, the storage and distribution systems should minimize the degradation of the water quality prior to use. After any such storage, testing should be carried out routinely and in accordance with a defined procedure. The storage and distribution of drinking-water should be done in a manner to ensure a turnover or recirculation of the water, if possible.

4.2.13 The equipment and systems used to produce and store drinking-water should be able to be drained or flushed, and sanitized.

4.2.14 Storage tanks should be closed with appropriately protected vents and should allow for visual inspection.

4.2.15 Distribution pipework should be able to be drained or flushed and sanitized.

4.2.16 The scope and extent of commissioning and qualification for the system should be identified and justified.

4.2.17 The results from testing drinking-water should be subjected to statistical analysis in order to identify trends and changes. If the drinking-water quality changes significantly, but is still within specification, the direct use of this water as a WPU, or as the feedwater to downstream treatment stages, should be reviewed for any potential risks. The appropriate action should be taken and documented.

4.2.18 Changes to a system or to its operation should be made in accordance with change control procedures.

4.2.19 Additional testing should be considered if there is any change in the raw water source, treatment techniques or system configuration.

4.3 **Bulk purified water**

4.3.1 Bulk purified water (BPW) should meet the relevant pharmacopoeial specifications for chemical and microbiological purity.

4.3.2 BPW should be prepared from drinking-water as a minimum-quality feedwater.

4.3.3 Any appropriate, qualified purification technique, or sequence of techniques, may be used to prepare BPW. BPW may be prepared by, for example, a combination of ion exchange, reverse osmosis (RO), RO/electro-deionization (EDI), and ultrafiltration.
4.3.4 The following should be considered when configuring a water purification system or defining user requirement specifications (URS):

- the quality of feedwater and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;
- unit process steps provided and documented with the appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity and total organic carbon;
- material of construction;
- sanitization strategy;
- main components;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

4.3.5 Ambient-temperature systems such as ion exchange, RO and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. Sanitization at defined intervals (e.g. based on the data collected from the system validation and system behaviour), as well as other controls, should be defined to prevent and minimize microbiological contamination.

4.3.6 Methods for sanitizing each stage of purification should be appropriate and validated. Where agents are used for sanitization, their removal should be validated.

4.3.7 The following controls should be considered in order to minimize and prevent microbial contamination:

- the maintenance of water flow at all times in order to prevent water from stagnating;
- control of temperature in the system, for example, by heat exchangers or room cooling in order to reduce the risk of microbial growth;
- the provision of ultraviolet disinfection at appropriate locations in the system;
- the use of water-treatment system components that can periodically be thermally sanitized above 70 °C for a defined period of time, or chemically sanitized using, for example, ozone, hydrogen peroxide and/or peracetic acid; and
- a combination of thermal and chemical sanitization, if required.
4.3.8 BPW should have appropriate alert and action limits for chemical and microbiological purity determined from a knowledge of the system and data trending. BPW should be protected from recontamination and microbial proliferation.

4.4 Bulk water for injections

4.4.1 BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxins). BWFI is the highest quality of pharmacopoeial WPU.

4.4.2 BWFI is not a final dosage form. It is an intermediate bulk product suitable to be used as an ingredient during formulation.

4.4.3 As a robust technique should be used for the production of BWFI, the following should be considered when configuring a water purification system or defining URS:

- the quality of feedwater and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required, where appropriate;
- based on the selection of components, material of construction and type of system, the appropriate URS, qualification and validation;
- the optimum generator size or generators with variable control to avoid over-frequent start/stop cycling;
- blow-down and dump functions;
- cool-down venting to avoid contamination ingress;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;
- appropriate instrumentation to measure parameters as required;
- sanitization strategy;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

4.4.4 BWFI may be prepared, for example, by distillation as the final purification step. Alternatively, BWFI may be produced by means other than distillation. Techniques such as deionisation, electro deionization, nano filtration, ultrafiltration, water softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a single or double pass RO system. For full details, see Production of water for injection by means other than distillation as published in the WHO Technical Report Series, No. 1025, Annex 3, 2020 (6).
4.4.5 BWFI should have appropriate microbial and chemical alert and action limits and should also be protected from recontamination and microbial proliferation.

4.5 Other grades of water

4.5.1 When a specific process requires a special non-pharmacopoeial grade of water, its specification must be documented within a company’s quality system. As a minimum, it must meet the pharmacopoeial requirements relating to the grade of WPU required for the type of dosage form or process step.

5. General considerations for water purification systems

5.1 Pharmaceutical manufacturers should apply the current principles of quality risk management (7) in selecting and using the appropriate water purification systems. An appropriate method for the production of WPU should be used.

5.2 Risks and controls should be identified for each stage of the production, storage, distribution, use and monitoring of WPU.

5.3 Risks identified should be evaluated in order to determine the scope and extent of validation and qualification of the system, including the computerized systems used for the production, control and monitoring of WPU.

5.4 Risk management should be an ongoing part of the quality management process for WPU. A mechanism to review or monitor events associated with the production, storage, distribution and use of WPU should be implemented.

5.5 Procedures for managing changes and deviations should be followed. Where applicable, the appropriate risk and impact assessments should be carried out where changes and deviations are managed.
5.6 The chosen water purification system, method or sequence of purification steps must be appropriate in order to ensure the production of water of the intended grade. Based on the outcome of the risk assessment, the following should at least be considered when selecting the water treatment system and method:

- the quality of the available feedwater and the variation over time (seasonal changes);
- the availability of suitable support facilities for the system (e.g. electricity, heating, steam, chilled water and compressed air);
- the extent of pre-treatment required;
- the sequence of purification steps required;
- the design and location of sampling points;
- the sanitization strategy;
- the availability of water-treatment equipment on the market;
- the reliability and robustness of the water-treatment equipment in operation;
- the yield or efficiency of the purification system;
- the ability to adequately support and maintain the water purification equipment;
- the continuity of operational usage considering hours/days/years and planned downtime;
- the total life-cycle of the system (including capital, operation and maintenance);
- the final water quality specification; and
- the minimum, average and maximum quantity of water required by the user.

5.7 The specifications for water purification equipment, storage and distribution systems should take into account the following:

- the location of the plant room;
- the extremes in temperature that the system will encounter;
- the risk of contamination, for example, from materials of construction (contact materials) and the environment;
- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;
- corrosion resistance;
- freedom from leakage;
- system configuration to avoid or minimize proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and/or chemical);
- the sanitization strategy;
- system capacity and output requirements; and
- the provision of all necessary instruments, test and sampling points in order to allow for all the relevant critical quality parameters of the complete system to be monitored.
5.8 The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

- the ability to collect samples;
- the space available for the installation and environment around the system;
- structural loadings on buildings;
- the provision of adequate access for maintenance and monitoring; and
- the ability to safely handle regeneration and sanitization chemicals.

6. Water storage and distribution systems

6.1 Where drinking water is stored and distributed, the appropriate controls should be determined and implemented in order to mitigate risks. This applies to all stages in the supply, storage and distribution of drinking-water.

6.2 The water storage and distribution systems for PW and BWFI should be appropriately designed, installed, qualified, operated and maintained in order to ensure the storage and distribution of water is of consistent quality to the user points.

7. Good practices for water systems

7.1 The components of water systems, including but not limited to pipework, valves and fittings, seals, diaphragms and instruments, should be appropriate and should satisfy the following objectives for the full range of the working temperature and potential chemicals that will come into contact with the system at rest, in operation and during sanitization. The construction materials should be of an appropriate quality.

7.2.1 As a minimum, the following design and construction practices should be considered.

For drinking water storage, supply and distribution systems on-site

Materials of construction should be selected based on the following requirements:

- ability to operate at the temperatures/pressures required;
- lack of impact to the final water quality;
- resistant to any sanitizing chemicals that may be used;
- threaded and flanged joints are permitted; and
- sample valves should preferably be of sanitary design.

Note that the system may have a design life at the end of which it should be replaced/adequately maintained.
For purified water and bulk water for injection systems

Note: Construction standards are generally aligned with potable water standards up to the process stage.

- Materials of construction should be appropriate. It should be non-leaching, non-adsorbing, non-absorbing and resistant to corrosion. Stainless-steel grade 316L or PVDC is generally recommended. The choice of material should take into account the intended sanitization method.
- Stainless steel systems should be orbitally welded, with manual welds where necessary. Inter-weldability between materials should be demonstrated with the maintenance of weld quality through a defined process. Documentation for such a system should be kept and should include, as a minimum, the qualification of the welder, welder set-up, work session test pieces (coupons or weld samples), proof of quality of gas used, welding machine calibration record, weld identification and heat numbers, and logs of all welds. Records, photographs or videos of inspection of a defined proportion of welds (e.g. 100% manual welds, 10% orbital welds).
- Joints should be made using sanitary connections, for example, Tri-clover joints. Threaded joints should not be permitted. Polyvinylidene fluoride or polyvinylidene difluoride (PVDF) systems should be fusion joined and visually inspected.
- Passivation should be considered for stainless steel systems, for example, for non-electropolished surfaces (after initial installation and after significant modification) in accordance with a documented procedure defining the solution to be used, its concentration, the temperature and contact time.
- Internal finish should be smooth.
- Flanges, unions and valves should be of a hygienic or sanitary design. Valves should be diaphragm type forged or machined body, with points of use constructed so that they can drain. Sample valves should be sanitary type with the surface roughness of 1.0 micron for PW and WFI systems and are typically installed between process stages and on the distribution loop return. The appropriate checks should be carried out in order to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly.
- The system should be installed to promote drainability with a recommended minimum slope of 1/100.
- Where appropriate, pressure or hydro-tests for leaks, spray-ball functionality test and flow turbulence should be considered.
- Provision should be made for on-line measurement for total organic carbon (TOC), conductivity and temperature.
Documents should provide evidence of system components and qualification. These include as applicable drawings, original or certified copies of certificates of conformity for materials of construction, records of on-site tests performed, weld/joining records, calibration certificates, system pressure test records and records of passivation.

8. System sanitization and bioburden control

8.1 Water-treatment, storage and distribution systems should be subjected to controls that will reduce the risk of contamination and the proliferation of microbiological organisms.

8.2 Controls may include using chemical and/or thermal sanitization procedures as appropriate (e.g. production, storage and distribution). The procedure and conditions used, such as times and temperatures, as well as the frequency, should be defined and proven to be effective for sanitizing all relevant parts of the system. The techniques employed should be considered during the design stage of the system as the procedure and technique may impact on the components and materials of construction.

8.3 Systems that operate and are maintained at elevated temperatures (e.g. > 70 °C) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed, or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress of contaminants including microorganisms (see section 9.2 for guidance).

8.4 Where the chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed in order to ensure that the sanitizing process selected is effective and that the sanitizing agent has been effectively removed.

8.5 Records of sanitization should be maintained.
8.6 Other control techniques to be considered may include:

- The maintenance of a continuous circulation of water maintaining turbulent flow evidenced by, for example, a Reynolds number of > 4000.
- Ensuring hygienic design, including the use of zero dead leg diaphragm valves and minimizing dead legs. Areas of possible dead legs should be measured and calculated.
- Installing pipework in a manner to allow for full drainage, if required. A guidance figure for the slope is not less than 1:100.
- Considering the use of ultraviolet lamps in the system where needed with independent monitoring.
- Maintaining the system at an elevated temperature (e.g. > 70 °C), if required.

9. Storage vessels

9.1 Storage vessels should be appropriate for their intended use.

9.2 As a minimum, the following should be considered:

- the design and shape;
- the provision for drainage of water from the vessel, when required;
- construction materials;
- capacity, including buffer capacity, between the steady state, water generation rate and the potentially variable simultaneous demand from user points, short-term reserve capacity in the event of failure of the water-treatment system or the inability to produce water (e.g. due to a regeneration cycle);
- prevention of stagnant water in the vessel (e.g. the headspace where water droplets can accumulate) and the need for the use of a spray-ball or distributor devices to wet the inner surfaces of the vessel;
- limitation and design of nozzles within the storage vessels;
- the fitting of bacteria-retentive, hydrophobic vent filters which are tested for their integrity at appropriate intervals;
- the fitting of sanitary design bursting discs provided with external rupture indicators to ensure that loss of system integrity is detected;
- the design and sanitization, as required, of level indicators;
- the design and location of valves, sampling points and monitoring devices and sensors; and
- the need for heat exchangers or jacketed vessels. Where these are used, double tube sheet or double plate heat exchangers should be used, ideally with the utility pressure less than the system pressure to minimise the risk of contamination.
10. **Water distribution**

10.1 The water distribution system should be designed as a loop, with continuous circulation of BPW and BWFI. Where this is not the case, the appropriate justification for using a non-recirculating one-way system should be provided as well as robust measures implemented to monitor these.

10.2 As a minimum, the following should be considered:
- controls to minimize proliferation of contaminants;
- material of construction, joints and impact as a result of sanitization; and
- the design and location of devices, sensors and instruments such as flow meters, conductivity sensors, TOC analysers and temperature sensors.

10.3 Filtration should not be used in distribution loops or at take-off user points.

10.4 Where heat exchangers are used, they should be arranged in continually circulating loops or sub-loops in order to avoid unacceptable static water in the system.

10.5 When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

10.6 Circulation pumps should be of a sanitary design with the appropriate seals to prevent contamination of the system.

10.7 Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

10.8 Consideration should be given to preventing contamination in systems where parallel pumps are used, especially if there is stagnant water when one of the pumps is not being used.
11. **Operational considerations including some qualification and validation principles**

11.1 Water systems should be appropriately qualified and validated (8). The scope and extent of qualification should be determined based on risk assessment.

11.2 When commissioning work is done, this should be documented. Commissioning is not a replacement for qualification.

11.3 In order to demonstrate the reliability and robustness of a system and its performance, a three-phase approach should be used for validation, covering at least one year of operation over different seasons. Tests on the source water (drinking-water) should be included within the validation programme and continued as part of the routine monitoring, and these results should meet specifications.

**Phase 1**

Phase I should cover a period of at least two weeks.

Operational procedures and schedules should cover at least the following activities and testing approaches:

- chemical and microbiological testing in accordance with a defined plan;
- sample, test and monitoring of the incoming feedwater to verify its quality;
- sample, test and monitoring after each step in the purification process;
- sample, test and monitoring at each point of use and at other defined sample points including the end of the distribution loop;
- verification of operating ranges;
- demonstrate performance of operating, cleaning, sanitizing and maintenance procedures;
- demonstrate the consistent production and delivery of product water of the required quality and quantity;
- provisional alert and action levels; and
- test-failure procedure.

The system should be monitored intensively for its performance. Water should not be used for product manufacturing during this phase.
Phase 2

Phase 2 should cover at least a further test period of two weeks after the satisfactory completion of Phase 1. The system should be monitored while deploying all the standard operating procedures (SOPs). The sampling program should be generally the same as in Phase 1. The use of the water for product manufacturing purposes during this phase may be acceptable, provided that Phase 1 and Phase 2 data demonstrate the appropriate water quality and the practice is approved by QA.

The approach should also:
- demonstrate consistent system operation within established ranges; and
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3

Phase 3 should cover at least a further 12 months after the satisfactory completion of Phase 2. The sample locations, sampling frequencies and tests may be reduced according to a routine plan which should be based on the established procedures and data from Phase 1 and Phase 2. Data should be trended, for example, quarterly and a system review should be undertaken after the completion of Phase 3 as part of the evaluation of system performance capability. The appropriate action should be taken where such a need is identified.

Water can be used during this phase. The data and information obtained during Phase 3 should demonstrate the reliable performance of the system over this period of time covering the different seasons.

12. Continuous system monitoring

12.1 The system should be subject to continuous monitoring.

12.2 A monitoring plan should be followed where samples are collected in accordance with a written procedure.

12.3 A combination of online and offline instruments, linked to appropriately qualified alarm systems, should be used. Parameters such as flow, pressure, temperature, conductivity and TOC should be monitored with online devices with periodic offline testing to confirm the results. Other parameters may be monitored through offline testing.
12.4 Offline testing (including physical, chemical and microbiological attributes) should be done in accordance with a predetermined programme.

12.5 Samples should be taken from points of use and dedicated sample points where required. All water samples should be taken using the same methodology as detailed in production procedures, for example, using a hose and with a suitable flushing and drainage procedure in place.

12.6 Tests should be carried out to ensure that the relevant pharmacopoeia specification (and approved company specification, where applicable) has been met. This may include the microbiological quality of water, as appropriate.

12.7 The results for identified quality attributes should be subjected to statistical analysis at defined intervals, for example, monthly, quarterly and annually, in order to identify trends. The results should be within defined control limits, such as 3 sigma.

12.8 Alert and action levels should be established based on historically reported data.

12.9 Adverse trends and out-of-limit results should be investigated for the root cause, followed by the appropriate corrective and preventive actions.

13. Maintenance of water systems

13.1 WPU systems should be maintained in accordance with an approved and documented maintenance programme. Records should be kept.

13.2 The programme should take into account at least the following:
  • defined frequency for system elements;
  • the calibration programme;
  • SOPs for specific tasks;
  • the control of approved spare parts;
  • preventive maintenance and maintenance plan and instructions, including cleaning after maintenance;
  • a review and approval of systems for use upon completion of work; and
  • a record and review of problems and faults during maintenance
14. **System reviews**

14.1 WPU systems should be reviewed at described intervals.

14.2 The review team should be comprised of representatives from, for example, engineering, utilities, validation, QA, quality control, microbiology, production and maintenance.

14.3 Examples of matters to be included in the review are:

- changes made since the last review;
- system performance trends and capability;
- quality trends;
- failure events and alarm history;
- investigations;
- out-of-specification and out-of-limit results;
- alert and action limits;
- assessing compliance with current GMP requirements for WPU systems;
- verification of documentation being current;
- records such as log books and electronic data; and
- the appropriateness of the software and the computerized system linked to the water system, for example, SCADA (Supervisory Control and Data Acquisition), including audit trail, authorized users with access and privileges.

15. **Inspection of water systems**

15.1 WPU (BPW and BWFI) systems are subjected to regulatory inspections. Users should conduct audits and self-inspection of water systems at regular intervals. Records should be maintained.

15.2 This document can be used as the basis of an audit and inspection. A tour of the water system, treatment system, storage and distribution system, as well as visible pipework and user points, should be performed to ensure that the system is appropriately designed, installed, qualified, validated, maintained and monitored.
Glossary

Commissioning. The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

References


Further reading

[Note from WHO Secretariat: will be updated further]

- European Pharmacopoeia: see website for the publishers of the European Pharmacopoeia and supplements (http://www.pheur.org/).
• World Health Organization, 2018. Developing drinking-water quality regulations and standards: general guidance with a special focus on countries with limited resources (https://apps.who.int/iris/bitstream/handle/10665/272969/9789241513944-eng.pdf?ua=1).

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REVISION OF CHAPTER 2.1:
GENERAL IDENTIFICATION TESTS

Draft proposal for revision in The International Pharmacopoeia

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by 18 September 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

[Note from the Secretariat. It is proposed to revise chapter 2.1: General identification tests. Changes from the current text are indicated in the text by insert or delete.]
REVISION OF CHAPTER 2.1:
GENERAL IDENTIFICATION TESTS

2.1 General identification tests

**Acetylated substances**
Place a quantity of the test substance as specified in the monograph in a test tube (of maximum 18 mm diameter) and treat it with 3 drops of phosphoric acid (~1440 g/L) TS. Close the tube with a stopper through which passes a smaller test tube filled with water and, on the outside of which, hangs a drop of lanthanum nitrate (30 g/L) TS. Heat the apparatus in a boiling water bath for 5 minutes. Transfer the drop of lanthanum nitrate to a white porcelain spot plate and mix with a drop of iodine (0.02 mol/L) VS. Place at the edge of the mixture a drop of ammonia (~100 g/L) TS. A blue colour slowly appears at the interface of the two liquids and persists for a short time.

**Amines, primary aromatic**
Dissolve a quantity of the test substance as specified in the monograph in 2 mL of hydrochloric acid (~70 g/L) TS with the aid of heat, if necessary. Cool in ice, treat it with 4 mL of sodium nitrite (10 g/L) TS and pour the mixture into 2 mL of 2-naphthol TS1 containing 1 g of sodium acetate R. A heavy precipitate, coloured as specified in the monograph, is produced.

**Ammonia and volatile aliphatic amines**
Dissolve a quantity of the substance as specified in the monograph, place the solution in a test-tube and add 1 g of magnesium oxide R; warm, if specified in the monograph. Alkaline vapours evolve gradually and turn manganese/silver paper R black, the reagent paper being placed in the upper part of the test-tube.

**Ammonium**
Carry out the test in an apparatus consisting of stoppered test-tubes A and B connected by a bent glass tube to permit a stream of air to pass consecutively through test-tubes A and B. Place the solution as specified in the monograph and 0.2 g of magnesium oxide R into test-tube A, and 1 mL of hydrochloric acid (0.1 mol/l) VS containing 1 drop of methyl red/ethanol TS in test-tube B. Bubble air through the apparatus. Evolved ammonia turns the colour of the solution in test-tube B to yellow. On the addition of 1 mL of sodium cobaltinitrite (100 g/l) TS to this solution a yellowish brown precipitate is formed.
**Bismuth**
A. Prepare the solution in hydrochloric acid (~250 g/l) TS as specified in the monograph and dilute 10 times with water. A white precipitate is formed, which turns dark brown on the addition of sodium sulfide TS.

B. Treat the solution in nitric acid (~1000 g/l) TS as specified in the monograph with potassium iodide (80 g/l) TS. A black precipitate is formed, which is soluble in an excess of the reagent to give a yellowish brown or orange solution. Dilute this solution with several volumes of water and heat; an orange or copper-coloured precipitate is obtained. The black precipitate that is first formed on the addition of potassium iodide (80 g/l) TS also becomes orange or copper-coloured when heated with water.

**Bromides**
A. Prepare a solution as specified in the monograph, acidify with nitric acid (~130 g/L) TS and add silver nitrate (40 g/L) TS. A yellowish curdy precipitate is produced, which is partially soluble in ammonia (~260 g/L) TS, but almost insoluble in ammonia (~100 g/L) TS and in nitric acid (~1000 g/L) TS.

B. **NOTE:** For testing bromides or hydrobromides of insoluble or sparingly soluble bases. Prepare the solution as specified in the monograph, add ammonia (~100 g/L) TS, filter, acidify the filtrate with nitric acid (~130 g/L) TS and proceed with test A.

C. Prepare the solution as specified in the monograph, acidify with sulfuric acid (~100 g/L) TS, and mix with chlorine TS. A brown solution results; after shaking with dichloromethane chloroform R, it becomes colourless whereas the dichloromethane chloroform layer turns reddish.

**Calcium**
A. Prepare the solution as specified in the monograph and add to it ammonium oxalate (25 g/L) TS. A white precipitate is formed, which is soluble in hydrochloric acid (~250 g/L) TS but is practically insoluble in acetic acid (~300 g/L) TS.

B. Treat 1 drop of a solution as specified in the monograph with 4 drops of glyoxal bis(2-hydroxyanil) TS, and 1 drop of sodium hydroxide (~80 g/L) TS. A reddish brown precipitate is formed which dissolves in dichloromethane chloroform R to give a red solution.
Chlorides
A. Prepare a solution as specified in the monograph, acidify with nitric acid (~130 g/L) TS and add silver nitrate (40 g/L) TS. A white curdy precipitate is produced, which is soluble in ammonia (~100 g/L) TS but is practically insoluble in nitric acid (~1000 g/L) TS.
B. NOTE: For testing chlorides or hydrochlorides of insoluble or sparingly soluble bases. Prepare the solution as specified in the monograph, add ammonia (~100 g/L) TS, filter and acidify the filtrate with nitric acid (~130 g/L) TS and proceed with test A.
C. Mix the quantity of the test substance as specified in the monograph with an equal quantity of manganese dioxide R, moisten with sulfuric acid (~1760 g/L) TS and heat gently. The evolved chlorine is recognizable by its greenish colour and produces a blue coloration of moistened starch/iodide paper R. Carry out the reaction preferably under a hood.

Citrate
A. Treat at ambient temperature a neutral solution as specified in the monograph with calcium chloride (55 g/L) TS. No precipitate is formed but, on boiling, a white solid is produced which is soluble in acetic acid (~300 g/L) TS.
B. Boil a solution with mercuric sulfate TS as specified in the monograph and filter if necessary. After the addition of a few drops of potassium permanganate (10 g/l) TS to the filtrate, the colour is discharged and a white precipitate is produced.
B. To 10 mg of the test substance or the solution described in the monograph, add 4 mL of pyridine R and 2 mL of acetic anhydride R, and shake; a yellow colour is immediately produced. Heat on a water bath for 2 minutes; a light pink to red colour is produced.

[Note from the Secretariat. Identity test C in the monograph on Diethycarbamazine dihydrogen citrate tablets describes a colour reaction using mercuric sulfate. It is proposed to replace the text by the following: Filter the aqueous layer obtained from identity test B. The filtrate yields reaction B described under 2.1 General identification tests as characteristic of citrates.]

Ferric salts:
Dissolve a quantity of the test substance to be examined equivalent to not less than 1 mg of iron (Fe3+) in 1 mL of water R or use 1 mL of the prescribed solution. Add 1 mL of potassium ferrocyanide (~53 g/L) TS. A blue precipitate is formed that does not dissolve on addition of 5 mL of hydrochloric acid (~70 g/L) TS.
**Ferrous salts**

A. Prepare a solution as specified in the monograph and add potassium ferricyanide (10 g/L) TS. A dark-blue precipitate is formed which is practically insoluble in hydrochloric acid (~70 g/L) TS.

B. Prepare a solution as specified in the monograph, acidify with sulfuric acid (~100 g/L) TS and treat with o-phenanthroline (1 g/L) TS. An intense red colour is produced which is discharged by the addition of ceric sulfate (35 g/L) TS.

**Iodides**

A. Prepare a solution as specified in the monograph, acidify with nitric acid (~130 g/L) TS and add silver nitrate (40 g/L) TS. A yellow curdy precipitate is formed which is practically insoluble in ammonia (~100 g/L) TS and in nitric acid (~1000 g/L) TS.

B. **NOTE: For testing iodides of insoluble or sparingly soluble bases.** Prepare a solution as specified in the monograph, add ammonia (~100 g/L) TS, filter and acidify the filtrate with nitric acid (~130 g/L) TS and proceed with test A.

C. Prepare a solution as specified in the monograph, acidify with sulfuric acid (~100 g/L) TS and add potassium nitrite (100 g/L) TS. A brown solution results; after shaking with dichloromethane chloroform R, it becomes colourless whereas the dichloromethane chloroform layer turns violet.

**Nitrates**

A. Prepare a solution as specified in the monograph and treat it with ferrous sulfate (15 g/L) TS. No brown colour appears unless sulfuric acid (~1760 g/L) TS is cautiously added to form a lower layer. A brown colour is then produced at the interface of the two liquids.

B. Add 2 mg of the finely ground test substance to a mixture of 0.1 mL of nitrobenzene R and 0.2 mL of sulfuric acid (~1760 g/L) TS. Allow to stand at room temperature for 5 minutes, cool in ice, and add slowly while mixing 5 mL of water and 3 mL of sodium hydroxide (~400 g/L) TS. Add 5 mL of acetone R, shake and allow to separate. An intense violet colour is produced in the upper phase.
Orthophosphates

A. Add, drop by drop, a quantity of nitric acid (~130 g/L) TS to 5 mL of ammonium molybdate (95 g/L) TS until any precipitate that may appear dissolves. Divide this solution into 2 portions, add to one portion a test solution acidified with nitric acid (~130 g/L) TS as specified in the monograph and boil both portions. A yellow precipitate is formed with the test solution while the other shows no more than a slight opalescence.

B. Prepare a neutral solution as specified in the monograph and add silver nitrate (40 g/L) TS. A yellow precipitate is produced which does not darken upon heating the solution to boiling. The precipitate is soluble in ammonia (~100 g/L) TS and in nitric acid (~130 g/L) TS.

Potassium

Prepare an alkaline solution as specified in the monograph and treat it with sodium tetraphenylborate (30 g/L) TS. A white precipitate is produced.

Salicylates

Treat a neutral solution as specified in the monograph with ferric chloride (25 g/L) TS. An intense reddish violet colour appears which remains on the addition of a small amount of acetic acid (~300 g/L) TS but disappears on the addition of hydrochloric acid (~70 g/L) TS, with separation of a white crystalline precipitate.

Sodium

A. Moisten a quantity of the substance with hydrochloric acid (~250 g/L) TS. An intense yellow colour is produced when the solution is introduced into a nonluminous flame. 

NOTE: Perform test B or C if, for technical reasons, test A cannot be carried out.

B. Acidify a solution as specified in the monograph with acetic acid (~60 g/l) TS, filter, if necessary, and treat it with uranyl/zinc acetate TS. A yellow crystalline precipitate is produced.

B. Dissolve 0.1 g of the test substance in 2 mL of water R or use 2 mL of the solution described in the monograph. Add 2 mL of potassium carbonate (150 g/L) TS and heat to boiling. No precipitate is formed. Add 4 mL of potassium pyroantimonate (13 g/L) TS and heat to boiling. Allow to cool in iced water and, if necessary, rub the inside of the test tube with a glass rod. A dense white precipitate is produced.

C. Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium (Na+) in 0.5 mL of water R or use 0.5 mL of the prescribed solution. Add 1.5 mL of methoxyphenylacetic R and cool in ice-water for 30 min. A voluminous, white, crystalline precipitate is produced. Place in water at 20 °C and stir for 5 min. The precipitate does not disappear. Add 1 mL of ammonia (~100 g/L) TS. The precipitate dissolves completely. Add 1 mL of ammonium carbonate solution R. No precipitate is produced.
Sulfates
A. Prepare a solution as specified in the monograph and add barium chloride (50 g/L) TS. A white precipitate is formed which is practically insoluble in hydrochloric acid (~250 g/L) TS.
B. To a solution as specified in the monograph, add lead acetate (80 g/L) TS. A white precipitate is formed which is soluble in ammonium acetate (80 g/L) TS and in sodium hydroxide (~80 g/L) TS but practically insoluble in hot water.

Tartrates
A. Acidify a solution as specified in the monograph with acetic acid (~300 g/L) TS and add 1 drop of ferrous sulfate (15 g/L) TS, a few drops of hydrogen peroxide (~60 g/L) TS and enough sodium hydroxide (~80 g/L) TS to make the solution alkaline. A purple or violet colour is produced.
B. Mix a few mL of sulfuric acid (~1760 g/L) TS with a few drops of resorcinol (20 g/L) TS and a few drops of potassium bromide (100 g/L) TS and add 2 or 3 drops of a solution as specified in the monograph. Warm the liquid in a water-bath for 5 to 10 minutes. An intense blue colour is produced. Cool the liquid and pour it into water. The solution becomes red.

Reagents to be added:
Ammonium carbonate (158 g/L) TS
Ammonium carbonate dissolved in water R to contain 158 g of ammonium carbonate R in 1000 mL.

Methoxyphenylacetic R
Procedure. Dissolve 2.7 g of methoxyphenylacetic acid R in 6 mL of tetramethylammonium hydroxide (~100 g/L) TS and add 20 mL of dehydrated ethanol R.
Storage. Store in a polyethylene container.

Methoxyphenylacetic acid R
C_{9}H_{10}O_{3}
Description. White, crystalline powder or white or almost white crystals.
Solubility. Sparingly soluble in water, freely soluble in ethanol (~750 g/L) TS.
Melting point. About 70° C.

Potassium carbonate (150 g/L) TS
Procedure. Dissolve 15 g of anhydrous potassium carbonate R in 100 mL of water R.
Potassium pyroantimonate (13 g/L) TS
Dissolve 1.95 g of potassium pyroantimonate R in 95 mL of hot water R. Cool quickly and add a solution containing 2.5 g of potassium hydroxide R in 50 mL of water R and 1 mL of dilute sodium hydroxide (~85 g/L) TS. Allow to stand for 24 hours, filter and dilute to 150 mL with water R.

Potassium pyroantimonate R
K$_{2}$Sb(OH)$_{6}$

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

*Solubility.* Sparingly soluble in water R.
POLICY:
EVALUATING AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS WHO LISTED AUTHORITIES

DRAFT FOR COMMENTS

Please send any comments you may have to Mr Mohamed Refaat, Technical Officer, Regulatory Systems Strengthening, Regulation and Safety Unit (refaatm@who.int), with a copy to Yvonne Melounou (melounouy@who.int) by 15 September 2020. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonesi@who.int and your name will be added to our electronic mailing list.
POLICY:
EVALUATING AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS WHO LISTED AUTHORITIES

1. Introduction

This policy on the evaluation and designation of regulatory authorities as WHO Listed Authorities (WLA) was developed following broad public consultation and the review of written comments received from the publication of a concept note (1), which informed the drafting of a first version of the WLA policy and operational guidance, as well as international consultative meetings with Member States and interested stakeholders (2, 3). It also considers recommendations from the fifty-second meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) on the replacement of the term “stringent regulatory authority” with “WHO-listed Authority” (4). The ECSPP recommendations were based on comments received on the proposed elements of a replacement definition for Stringent Regulatory Authorities (SRAs) posted by WHO for public comment in August 2017 that was intended to provide a more transparent, robust and equitable measure of regulatory performance (5).

2. Context

World Health Assembly Resolution 67.20 (WHA 67.20) on Regulatory system strengthening for medical products (6) recognizes that effective regulatory systems are an essential component of health system strengthening, necessary for the implementation of universal health coverage and, ultimately, contribute to better public health outcomes. Resolution WHA 67.20 also recognizes that inefficient regulatory systems can be a barrier to access to safe, effective and quality medical products. Several WHO regional committee resolutions on regulatory system strengthening have also been adopted, including, for example, Regional Committee Resolution (CD50.R9), 2010, in the WHO Regional Office for the Americas (AMRO/PAHO) (7), Regional strategy for improving access to essential medicines in the Western Pacific Region (2005-2010) (8), and document AF/RC63/7 of the WHO Regional Office for Africa (AFRO) (9). The road map for access to medicines, vaccines and other health products highlights regulatory system strengthening as an integral part of a health systems approach to improving access to safe and effective medical products of assured quality (10).
Resolution WHA 67.20 calls upon WHO to:

a) apply evaluation tools to generate and analyse evidence of regulatory system performance;
b) facilitate the formulation and implementation of institutional development plans; and
c) provide technical support to national regulatory authorities and governments.

The WHO supports Member States in strengthening regulatory systems as a means of promoting equitable access to and availability of quality assured medical products. To assist countries in reaching and sustaining a level of medical product regulatory oversight that is effective, efficient and transparent, WHO has implemented a regulatory system strengthening programme. Its objectives are to:

a) promote regulatory cooperation, convergence and transparency through networking, work-sharing and reliance; and
b) build regulatory capacity in Member States consistent with good regulatory practices.

In order to reach these objectives, WHO has established the framework, principles, tools and processes to, among others, a) evaluate regulatory systems and establish maturity levels by applying the Global Benchmarking Tool (GBT) (11) and b) evaluate regulatory performance in order to designate authorities responsible for regulation of medical products as WLA.

3. Purpose

The principle of reliance is central to WHO’s approach to regulatory system strengthening and effective regulation, regardless of the size and maturity of the authority (12). Regulatory cooperation and reliance are built on trust and confidence which, in turn, depend on greater knowledge and transparency of the regulatory systems and the performance of the regulatory authority upon which others may rely.

The introduction of a framework for designating and publicly listing a regulatory authority as a WLA provides a transparent and evidence-based pathway for regulatory authorities to be globally recognized as meeting and applying WHO and other internationally recognized standards and guidelines, as well as good regulatory practices. The main purpose of the introduction of the WLA designation is the replacement of the concept of an SRA which was initially developed to guide global procurement of medicines. This concept has been used by the WHO Secretariat and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) to guide medicine procurement decisions and has subsequently become widely recognized by the international regulatory and procurement community.
The definition of an SRA, first published by the Global Fund in 2008, was based on membership in the International Conference (now Council) of Harmonization (ICH) (13) but the utilization of this concept has been documented since 2003. An interim definition adopted by ECSPP in 2017 restricted eligibility to ICH membership prior to 23 October 2015 while awaiting the development of a more suitable definition and approach based on the WHO benchmarking of regulatory systems (14).

The WLA framework is also replacing the concept and procedure for recognizing regulatory authorities exhibiting ‘a high level of performance’ in vaccine regulation based on criteria defined in the WHO Technical Report Series (TRS) 978 (15).

The GBT is and remains the foundation for assessing the regulatory systems based on inputs, processes and outputs. Based on this, the WLA framework is meant to provide a more detailed picture of how a regulatory system operates through an additional performance evaluation process that examines key regulatory outputs and consistency in adherence to international standards and guidelines as well as good regulatory practices.

It should be noted that in 2019, an estimated 75% of the 194 Member States were estimated to not have a stable and well-functioning regulatory system corresponding to maturity level (ML) 3 or 4, with ML 3 being the target of Resolution WHA 67.20. Bringing these regulatory systems to ML 3 will require significant and sustained efforts and a ‘smart’ regulatory approach based on reliance on other mature and trusted reference regulatory authorities – the WLAs – whenever possible.

The designation of a regulatory authority as a WLA is ultimately meant to promote access and the supply of safe, effective and quality medical products by facilitating the use of reliance on the work products and decisions of trusted agencies in the regulatory decision-making of regulatory authorities and the procurement decisions of the United Nations (UN) and other agencies to reduce the redundancy and waste of limited regulatory and financial resources.

4. **Scope**

This policy describes the purpose, definitions and operating principles related to the evaluation and public listing of authorities responsible for the regulation of medical products as WHO Listed Authorities or WLAs. The initial scope of the WLA designation will be limited to medicines and vaccines, with an option to expand to other categories of products in the future in line with the expansion of the scope of the GBT.
5. **Policy statement**

Independent, efficient, science-based and transparent regulatory systems are essential to health care systems, access to safe, effective and quality medical products and the implementation of universal health coverage. A system for publicly designating regulatory authorities as WLAs provides an evidence-based mechanism to evaluate, recognize and transparently classify and list well-performing regulatory systems. It thereby, where appropriate, intends to:

a) promote trust, confidence and reliance between regulatory authorities;
b) encourage continuous improvement of regulatory systems and the efficient use of regulatory resources;
c) expand the pool of regulatory authorities beyond SRAs for users such as regulatory authorities or the WHO Prequalification (PQ) Programme;
d) promote the supply of safe, effective and quality assured medical products for use by UN procurement agencies and countries; and
e) create an enabling environment for innovation and local production of medical products by facilitating the implementation of reliance approaches and therefore accelerating access to safe, effective and quality assured medical products.

6. **Definition of a WHO Listed Authority**

A WHO Listed Authority (WLA) is a regulatory authority\(^6\) or a regional regulatory system which has been documented to comply with all the indicators and requirements specified by WHO for listing based on an established benchmarking and performance evaluation process.

7. **Operating principles**

The following principles define in broad terms how the WLA framework is to be implemented. Details are provided in the *WLA Operational Guidance* and accompanying procedures.

a) The process to establish a WLA is initiated by a request from the Member State; for a regional regulatory system (RRS), the request should come from a regional body, where it exists, or another institution representing the RRS, following coordination with the individual authorities that are part of the system, as appropriate.

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\(^6\) A regulatory authority is meant to cover all the institutions, working together in an integrated and effective manner, that are responsible for the regulatory oversight of medical products in a given country or region.
b) The GBT forms the basis for evaluating the ML. The WLA performance evaluation process assesses the consistent performance including adherence to international standards and guidelines, as well as good regulatory practices of the regulatory authority or RRS over time against the requirements established for the scope of listing being sought.

c) A regulatory authority or RRS can be listed for one or more product categories and/or for one or more regulatory functions.

d) Regulatory authorities or RRSs must at least have attained overall ML 3 as established by the GBT to be eligible for consideration as a WLA.

e) A WLA is expected to have the capacity and established track record of performing the regulatory functions for the product categories relevant to the scope of the WLA listing. A WLA can rely in a targeted way based on a defined approach on others for these functions and/or products categories, but full reliance cannot be used as a substitute for reliable performance of regulatory functions/for product categories which are assessed as part of the listing.

f) After the WHO confirms eligibility criteria are met, the regulatory authority or the RRS and WHO agree to a written plan of performance evaluation and commit the necessary resources to execute the plan, which may be adjusted from time to time. The plan agreed, the resources involved and the time for execution of the plan will depend on the requested scope, the completeness of the documentation as well as the readiness of the regulatory authority or RRS.

g) In considering the extent and depth of the evaluation process, factors such as existing evidence and track record of regulatory function and performance, including from previous benchmarking/audit exercises undertaken by WHO or other organizations such as, for example, the Pharmaceutical Inspection Co-operation Scheme (PIC/S), Benchmarking of European Medicines Agencies (BEMA) or the International Organization for Standardization (ISO) of the regulatory authority or RRS, should be taken into consideration when determining compliance with the requirements for designation as a WLA in order to make best use of limited resources for performance evaluation and avoid unnecessary burden and ensure optimal use of resources.

h) The degree of integration on the basis of a common framework varies between different regional regulatory systems which should also be taken into account in the designation of these systems.

i) All non-public information provided is kept confidential.

j) Following the successful completion of the WLA evaluation process, a regulatory authority or RRS is publicly listed as a WLA in the list of reference authorities (16). The listing as a WLA includes the scope of the designation (product categories and/or regulatory functions); evidence reviewed, and the process undertaken to support the listing; the original date and the period of validity of the initial listing.
k) A listing will initially be valid for a period of 5 years unless extended. A risk-based process will be used to renew the initial listing. Once renewed, the listing will no longer be subject to a validity period but to a continuous monitoring based on risk management principles to ensure that requirements for the listing continue to be met.

l) Changes or events that could cause sufficient concern that the requirements for the listing are no longer met will trigger a re-evaluation of the WLA. The re-evaluation will be risk-based and will focus on the issues of concern.

m) To ensure impartiality of the WLA process, a recommendation to list or delist a regulatory authority or RRS is made following a review of the evaluation report on the candidate WLA by an advisory committee. This committee will be set up by WHO based on established and transparent criteria such as ensuring equitable geographical representation, gender balance and professional competencies in order to provide a representation of different approaches and practical experience from all regions of the world. The review process provides an additional level of assurance that due process was followed and that decisions are supported by findings.

n) WHO reserves the right to delist a WLA should, upon evaluation and subsequent discussion with the regulatory authority or RRS, it be concluded that the basis for supporting the listing is no longer valid. Delisting and the rationale for delisting are published on the WHO website. The decision to delist would follow a meeting with the regulatory authority or the RRS during which the authority would have an opportunity to present its case.

o) The ultimate responsibility and decision for use of the list resides with the users (e.g. regulatory authorities, WHO Prequalification Programme, procurement agencies) and depends on the specific context of its intended use.

The designation of WLAs is meant to substantiate the maturity level using an international benchmark, as defined by the GBT and the performance of regulatory authorities and RRSs using the WLA performance evaluation process. It is not meant to make any inference regarding the maturity or performance of a regulatory authority or RRS that has been evaluated by other institutions or through other procedures.
8. Glossary

Common regulatory framework. A common regulatory framework is a unified set of requirements, processes and controls applied in the supervision of medical products. For a common legal framework this is, in addition, underpinned by common legislation.

International standards and guidelines. For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant internationally recognized standards (e.g. ISO or pharmacopoeial standards) and guidelines (e.g. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) or PIC/S guidelines).

Maturity level (ML). The maturity of regulatory systems is divided into four levels, characterized as follows:

- **ML1**: some elements of regulatory systems exist;
- **ML2**: evolving national regulatory systems that partially perform essential regulatory functions;
- **ML3**: stable, well-functioning and integrated regulatory systems; and
- **ML4**: regulatory systems operating at advanced level of performance and continuous improvement.

Product category(ies). Refers to “medical products” which may include the following product categories: vaccines, medicines, medical devices including in-vitro diagnostics, blood and blood products and vector control products.

Regional regulatory system (RRS). A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework including or excluding a common legal framework. The common framework must at least ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework. A RRS so described may be considered a single entity and therefore eligible for listing as a WLA, as well as each of the individual authorities that are part of the system. In cases where a RRS is further underpinned by a common legal framework, it should be considered as a single entity and, as such, eligible for listing as a WLA, as well as each of the individual authorities that are part of the system.
**Regulatory function(s).** The term refers to the regulatory functions as components of a regulatory system for medical products defined in the GBT being national regulatory systems, registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight, and national regulatory authorities (NRA) lot release.

**Reliance.** The act whereby the (national) regulatory authority in one jurisdiction may take into account and give significant weight to assessments performed by another (national) regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable for decisions taken, even when it relies on the decisions and information of others.

**Stringent regulatory authority** (*interim definition ECSPP*). A regulatory authority which is:

a) a member of the ICH, being the European Commission, the United States (U.S.) Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan, also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or

b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or

c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) *(6).*
References


12. WHO Good Reliance Practices (GReIP) (link to document to be added after start of public consultation).


Good regulatory practices
for regulatory oversight of medical products

DRAFT FOR COMMENTS

Please send your comments to Dr Marie Valentin, Technical Officer, Regulatory Convergence and Networks, Regulation and Safety (valentinm@who.int), with a copy to Mrs Carolyn Doucelin (doucelinc@who.int) by 11 September 2020.

Please use our attached Comments Table for this purpose.
Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
Good regulatory practices
for regulatory oversight of medical products

Acronyms

APEC  Asia-Pacific Economic Cooperation
ASEAN  Association of Southeast Asian Nations
GGP   Good Governance Practices
GRP   Good Regulatory Practices
GReIP  Good Reliance Practices
GRevP  Good Review Practices
OECD  Organisation for Economic Co-operation and Development
QMS   Quality Management System
QRM   Quality Risk Management
WHO   World Health Organization
WLAs  WHO-Listed Authorities
Executive Summary

A fundamental role of government is to protect and promote the health and safety of the public, including the delivery of health care. A well-functioning health care system depends upon the availability and affordability of medical products that are safe, effective and of consistently assured quality.

The medical products sector is one of the most regulated of all industries as a consequence of the impact of the diverse range of medical products on health, the difficulty in assessing their quality, safety and efficacy, and the complexities associated with their development, production, supply and surveillance. It is therefore essential that the interests and safety of the public be entrusted to a regulatory body responsible for ensuring that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

Regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. A coherent legal framework should be established and implemented that provides the required level of oversight while also facilitating innovation and access to safe, effective and quality medical products. This also means building the necessary flexibilities and responsiveness to manage public health emergencies, address new technologies and practices and promote international regulatory cooperation.

Governments incur costs by establishing and maintaining regulatory systems to protect and promote the health of its citizens. Regulated parties incur costs in complying with regulation. However, additional impacts (health system, socio-economic and economic impacts) can accrue from inefficient regulatory systems - with potentially significant implications for disease morbidity/mortality, health care costs and the economy.

A sound legal framework, the adoption of international norms and standards and the recruitment and development of competent staff are necessary but not sufficient conditions to ensure 'good regulatory oversight'. These measures must be combined with good regulatory practices (GRP) that guide all individuals within organizations entrusted to regulate in the application of requirements and the formulation of decisions so that they are clear, consistent, impartial, proportionate, timely and based on sound science and legislation. GRP can be defined as a set of principles and practices that are applied to the development, implementation and maintenance of regulatory instruments – including laws, regulations and guidelines – in order to achieve a public health policy objective in the most efficient way.
The successful application of GRP is the hallmark of a modern, science-based and responsive regulatory system that translates the practice of regulation into desired outcomes. GRP provide a means of establishing and implementing sound, affordable and efficient regulatory oversight of medical products as an important part of health system performance and sustainability.

This document is intended to present Member States with widely-recognized principles of GRP. The principles presented in this document derive from an extensive review of public documents developed by governments and multi-lateral organizations on the subject, as well as many consultative workshops, benchmarking exercises and interactions with Member States. The nine principles presented in this document, such as, legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency and transparency, are relevant to all authorities responsible for the regulatory oversight of medical products, irrespective of resources, sophistication or regulatory model.

GRP serve as a foundation within a suite of related guidance documents on best regulatory practices. Taken together, this expanding set of guidance documents is intended to provide regulatory authorities comprehensive guidance on improving their performance. This document will be supplemented by practical ‘how to’ guides and tools designed to facilitate the implementation of GRP.
1. **Introduction**

This document responds to requests from national authorities responsible for the regulatory oversight of medical products for guidance in addressing common gaps in regulatory practices identified during benchmarking exercises.

This document draws upon documents from multilateral bodies such as the Asia-Pacific Economic Cooperation (APEC), the Organisation for Economic Co-operation and Development (OECD), the World Bank and the Association of Southeast Asian Nations (ASEAN) (1) (2) (3) (4) (5) as well as guides published by a number of governments. The document also takes account of earlier World Health Organization (WHO) documents that touch on aspects of GRP (6) (7) (8) (9) (10) (11) (12) (13) (14) and from WHO experience in applying the WHO Global Benchmarking Tool (GBT) and promoting the various principles of good regulatory practices (GRP).

When the principles of GRP are properly implemented through the GRP enablers across the regulatory system, desired regulatory outcomes and impact can be achieved.

2. **Background**

A fundamental role of government is to protect and promote the health and safety of the public, including in the delivery of health care. A well-functioning health care system depends upon the availability and affordability of medical products that are safe, effective and of assured quality.

Medical products are essential to the prevention, diagnosis and treatment of disease and the consequences of substandard and falsified medical products can be therefore life-threatening. This reality is of particular concern as users of medical products are typically not in a position to judge their quality. It is therefore essential that the interests and safety of the public be entrusted to a regulatory body or bodies responsible for ensuring that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

The regulatory oversight of medical product has become increasingly complex given the globalization of product development, production and supply, coupled with the rapid pace of technological and social change in a context of limited financial and human resources.
The importance of robust regulatory systems was recognized by the Sixty-Seventh World Health Assembly in endorsing Resolution WHA 67.20 Regulatory system strengthening for medical products. The Resolution notes that “effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes”, that “regulators are an essential part of the health workforce”, and that “inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products” (15).

A sound system of oversight requires that regulatory authorities are supported by an effective framework of laws, regulations and guidelines, and that they have the competence, capacity and science-based knowledge to conduct their mandate in an efficient and transparent manner. The degree to which the regulatory framework fulfils policy objectives depends on the quality of its development and implementation processes.

GRP are critical to the efficient performance of the regulatory system and, consequently, to the public’s confidence in the system. A sound regulatory framework, including the adoption of international norms and standards and the recruitment and development of competent staff, are necessary but not sufficient conditions to ensure ‘good oversight’. These measures must be combined with GRP that guide all individuals from regulatory authorities to set appropriate requirements and formulate decisions that are clear, consistent, impartial, proportionate, timely and based on sound science.

3. Purpose

This document presents the high-level principles of GRP. The principles are intended to serve as a benchmark and thereby assist Member States in the application of good practices for the regulatory oversight of medical products. This document is also meant to assist Member States in prioritizing the functions of a regulatory system based on available resources, national goals, medical products policies and the medical product environment. This principles-based document will be supplemented by practical ‘how to’ guides and tools designed to facilitate the implementation of GRP within organizations responsible for the regulatory oversight of medical products.

This foundational document is complemented by a suite of related guidance on best regulatory practices, including but not limited to good governance practices (GGP) (16), good reliance practices (GRelP) (17), good review practices (GRevP) (18) and the implementation of quality management systems (QMS) for national regulatory authorities (NRAs) (19). Taken together, this expanding body of work is intended to provide regulatory authorities with comprehensive guidance on improving performance.
4. **Scope**

This document is relevant to all regulatory authorities irrespective of resources, maturity or regulatory model. These GRP high-level principles are equally applicable to regulatory systems that are supranational (e.g. regional), national and/or subnational in nature, or involve multiple institutions charged with regulating certain products or activities within a country or jurisdiction.

This document presents principles and considerations in the development and implementation of regulatory instruments which underpin regulatory activities. Broader practices and attributes are presented that define well-performing regulatory systems for medical products.

This document is intended for a number of related audiences: institutions and policy-makers responsible for the formulation of health policies, laws, regulations and guidelines; institutions that, together, form national or supranational systems for regulatory oversight of medical products; regulatory networks and parties affected by or otherwise interested in regulatory frameworks; for example, industry or other developers of medical products.

5. **Objectives**

GRP provide a means of establishing sound and effective oversight of medical products as an important part of health system performance and sustainability. If consistently and effectively implemented, they can lead to higher quality regulation, improved regulatory decision-making and compliance, increased efficiency of regulatory systems, and better public health outcomes. They help to ensure that regulatory systems remain current as technologies and the systems in which they are used continue to evolve.

Within the context of an increasingly complex and interconnected regulatory environment, GRP are also an important enabler in promoting trust between regulatory authorities and thereby facilitating international cooperation and the adoption of more effective and efficient approaches to ensuring the quality, safety and efficacy of medical products within the global regulatory community.

The ultimate aim of GRP is to serve and protect public health and patients’ interest, respecting all applicable ethical principles.
6. Key considerations

The medical products sector is one of the most regulated of all industries as a consequence of the impact of the diverse range of medical products on health and society, the difficulty in assessing their quality, efficacy and safety, lessons learned from public health tragedies, and the complexities associated with developing, producing, supplying and monitoring medical products to ensure they consistently perform as intended. This has led many countries to put into place an increasingly sophisticated set of laws, regulations and guidelines that control all aspects of the medical product life-cycle.

While providing the necessary authorities, prohibitions and tools necessary to fulfil publicly entrusted mandates, regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. This means establishing and implementing a coherent regulatory framework that provides the required level of oversight and control while also facilitating the innovation and access to safe, effective and quality medical products. It also means building the necessary flexibilities and responsiveness to manage public health emergencies, address new technologies and best practices, and promote international regulatory cooperation.

Increasingly, policy makers and regulatory authorities must adopt modern and responsive models of regulation that consider resource constraints in the face of the challenges posed by scientific development, globalization, rising public expectations and public health emergencies.

Weak or inefficient regulatory systems can be a barrier to access to safe, effective and quality medical products and a threat to public health. At the same time, countries strengthen regulatory capacity regulatory systems need to be science-based, respect international standards and to adopt an approach that leverages the work of other trusted regulatory authorities and institutions whenever possible. Towards this end, countries are encouraged to formulate and implement policies and strategies that promote convergence, harmonization, information and work-sharing, and reliance as part of GRP (17). An ongoing initiative at WHO aims at establishing and implementing a framework for evaluating NRAs and regional regulatory systems as well as designating those that meet a specific standard as WHO-Listed Authorities (WLAs) (20).
For reasons of public health protection noted earlier in the document, the need for regulatory controls over medical products is fully acknowledged. The issue is more how to regulate in an effective, efficient and transparent manner, such that the interests of the health care system are served. The consistent application of GRP in all aspects of oversight is essential in ensuring that these interests are met and providing the foundation on which a well-performing, respected regulatory system is built.

GRP can be defined as a set of principles and practices that are applied to the development, implementation and maintenance of regulatory instruments – including laws, regulations and guidelines – in order to achieve a public health policy objective in the most efficient way.

GRP is about instilling a culture of best practices across institutions responsible for regulatory oversight to ensure that regulation is fairly, consistently and effectively applied.

7. Overview of regulatory system for medical products

Definitions are essential to a common understanding of concepts. While a more extensive set of terms is provided in the Glossary, an elaboration of the terms regulatory framework, legal framework, regulatory authority, regulatory system, and regulatory outputs is provided below to ensure a proper understanding of their usage in this document.

Components of the regulatory framework

In this document, the terms “law” and “regulation” are used for the components of the legal framework (binding legislation). It is acknowledged that other terms may be used in different jurisdictions, such as “act” (instead of law) or “ordinance” (instead of regulation).

Laws are generally used to set out at a high level the roles and responsibilities of institutions; in this case, the regulatory authority, the ministry of health and other relevant organizations. They define the products, persons and activities that are to be regulated and state what is permitted and what is not. More importantly, laws authorize the institution to make lower level (or subordinate) regulations.

Regulations are a diverse set of instruments by which governments place requirements on enterprises and citizens. The regulations usually state at high level the conditions to be met and detail the requirements defined in the laws.
For instance, a law may prohibit the manufacturer, importation or sale of a medical product in the absence of specific authorisation. The regulations would set out the conditions for obtaining authorisation; for example, the need to provide certain types of information - such as clinical trial and manufacturing and control data - that would allow the regulatory authority to establish the quality, safety and efficacy of a medical product.

*Guidelines (and other guidance documents)* provide further detail on how the regulated stakeholders can comply with the laws and regulations. Guidelines may also provide details on the processes that enforce the respective legislation (laws and regulations). Within a regulatory framework for medical products, these documents are usually non-binding and are generally more detailed and scientific in nature. This makes them appropriate for describing approaches generally considered suitable for satisfying regulatory requirements but unsuitable to be embedded into legislation.

![Architecture of a Regulatory Framework](image)

**Figure 1: Architecture of a Regulatory Framework**

**Components of the regulatory system**

A *regulatory authority* is a public institution(s) or governmental body/bodies authorized by law to independently exercise regulatory powers concerning the development, production, marketing and surveillance of medical products. Although the term implies that a single organization is responsible for all regulatory functions, indeed these functions may be undertaken by one or more institutions reporting to the same or different senior official. The regulatory authority plays a critical role in ensuring the quality, safety, efficacy and performance of medical products as well as the relevance and accuracy of product information.
The regulatory framework is the collection of laws, regulations, guidelines and other regulatory instruments through which a government and a regulatory authority controls particular aspects of a specific activity.

The legal framework is the part of the regulatory framework that refers to (binding) pieces of legislation, such as laws and regulations.

Regulatory outputs are the results or products coming from the regulatory authority (e.g. inspection/assessment reports, decisions, product label, and so on).

The term regulatory system is used to describe the combination of the institutions, processes, regulatory framework and resources which, taken together, are integral to the effective regulatory oversight of medical products in a given country or multi-country jurisdiction. GRP should be considered and applied for the whole regulatory system.

Figure 2: Principles and enablers of Good Regulatory Practices (GRP) and Components of the regulatory system
When looking at the overall regulatory system, three main components (inputs) can be seen as the main contributors to regulatory functions and activities: (1) regulatory framework composed of legal framework (laws and regulations) along with guidelines and other guidance documents, (2) regulatory institutions which may be represented by one or more entities including the national regulatory authority (NRA), the national control laboratory, pharmacovigilance centre(s), research ethics committee(s) and others, and (3) all types of resources including human and financial resources, infrastructure and equipment and information management systems. There are several regulatory outputs depending on the concerned functions and activities (e.g. regulatory and marketing authorization inspection/assessment reports). The concepts and principles of GRP cover and address the overall regulatory system as explained above. For the purpose of application and implementation of GRP, several enablers are essential (see 10. Enablers for Good Regulatory Practices). When the principles of GRP are properly implemented through the enablers, a desired regulatory outcome and impact can be achieved.

WHO classifies the spectrum of regulatory activities according to seven common regulatory functions applicable to the regulation of all medical products: clinical trials oversight, registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection and laboratory testing (21). In addition, a number of non-common functions apply to certain medical products, such as official lot release for vaccines and other biologicals.

The term regulatory authority implies that a single organization is responsible for all regulatory functions. This is not always the case. For example, different organizations may be legally responsible for the regulation of medicines and vaccines as compared to medical devices. Even when one body is responsible for all regulatory functions, aspects critical to certain functions may lay outside the authority, such as those performed by pharmacovigilance centres that have a formal relationship with the authority in collecting adverse event reports. Certain regulatory functions may also be undertaken by third parties, as in the case of auditing organizations in relation to medical devices.

Regulatory activities may also be undertaken at a supranational (e.g. regional), national and/or subnational level. Examples include the supranational evaluation of certain products for the purpose of granting a marketing authorization valid across multiple countries, or the GMP inspections of multi-source medicines performed at the state level.
8. Principles of good regulatory practices

There is no universal model for the regulatory oversight of medical products. Each approach will reflect national health policies and priorities, the country’s level of socioeconomic development, the availability of resources and infrastructure, the health system, the national legal system, the research and development capacity, as well as the local production capacity. Nonetheless, as in other regulated sectors, there is a growing international consensus on best practices that may be applied to regulatory oversight.

A review of public documents (1) (4) (5) (22) on GRP reveals common themes that should be adopted by all institutions responsible for or involved in the regulatory oversight of medical products. These principles apply equally to the development and implementation of regulatory oversight and to daily regulatory business.

GRP are guided by overarching principles. There are nine principles which are listed below and are described in this section, together with considerations relevant to the regulatory oversight of medical products.

Further elaboration of the principles, practices and examples is foreseen in supplemental ‘how to’ guidance complementing this document.

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<th>Principles of Good Regulatory Practice</th>
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Efficiency

Regulatory systems should achieve their goals within the required time and at reasonable effort and cost. International collaboration promotes efficiency by allowing the best use for resources.

Transparency

Regulatory systems should be transparent; requirements and decisions should be made known, and input sought on regulatory proposals.

8.1 Legality
Regulatory systems and the decisions that flow from them must have a sound legal basis.

Key elements:

- The regulatory framework should provide the necessary authorities, scope and flexibilities to safeguard and promote health.
- The delegation of power and responsibilities to different levels of the regulatory system should be clear and explicit.
- Regulatory frameworks should support and empower regulatory authorities to contribute to and benefit from international cooperation.
- Systems should be in place to ensure that regulatory decisions and sanctions can be reviewed.
- Regulatory framework should afford for the integrity of the regulatory system with clear scope and lines of authority of institutions forming the regulatory system.
- A legal framework must hold the regulatory authority accountable to the public, those regulated and the government for their actions and decisions.

The principle of legality means that the regulatory system is structured so that all regulatory actions and decisions are based on clear legal authority, thus respecting the “rule of law”.

A regulatory body exists to achieve objectives deemed by the government to be in the public interest. It must operate within and in accordance of the powers conferred by the legal framework (23). The law or act establishing the regulatory authority should be clear on the objectives of the enabling legislation, the powers of the authority, the scope of products and general activities the authority is mandated to regulate, and the provisions for making regulations.

The delegation of power and responsibilities to different levels of the regulatory system should be explicit and clear. When more than one institution or level of government is involved in the regulation of medical products, the functions and responsibilities of the various institutions should be clear and complementary (see 9.2 Consistency).
Given the need for all regulatory authorities to cooperate to manage increasingly complex and cross-jurisdictional issues, it is essential that a modern legal framework for medical products supports and encourages such cooperation in all its forms - including convergence, harmonization, information- and work-sharing, reliance and recognition. Ideally, this would take the form of explicit provisions in law and/or regulations, with further operational detail provided in policies and procedural guidance. At a minimum, the legal framework should not prohibit all forms of regulatory cooperation, including the use of assessments and decisions of other trusted regulatory authorities and institutions in performing its own work. Cooperation does not alter the sovereign responsibility and accountability of each regulatory authority to protect the health and safety of its citizens but allows for the exchange of good practices and may help save resources and avoid duplication.

Legislation has to be in place to control and perform all required regulatory activities under common and non common regulatory functions. Policies, guidelines and procedures cannot compensate for the absence of legislation.

A legal framework should support the integrity of the regulatory system with clear authority, power, roles and responsibilities of institutions forming the regulatory system. Conflict in organizational authority or responsibilities should be avoided.

All regulatory authorities must be accountable to the public, those regulated, and the government for their actions and decisions as part of good governance and accountability frameworks. Within the context of GRP, accountability means that regulatory authorities are: (i) responsible for acting according to certain standards and commitments; (ii) answerable for their actions; and (iii) willing to face the consequences when standards or commitments are not met.

Regulatory actions and decisions should be consistent with authorities and controls provided for by the legal framework. Processes should therefore be put in place for the review of regulatory decisions. This includes internal appeal mechanisms and the right to judicially appeal decisions of regulators – including on the grounds of procedural fairness and due process – in addition to scientific and administrative grounds.
8.2 Consistency
Regulatory oversight of medical products should be consistent with existing government policies and legislation and be applied in a consistent and predictable manner.

Key elements:
- The regulatory framework for medical products should fit coherently into the national legal and policy framework.
- New regulations should complement, and not conflict with, existing regulatory instruments.
- Regulatory requirements should be consistently implemented and enforced across medical product sectors and stakeholders.

Regulatory oversight of medical products must be performed in the context of, and in ways coherent with, the national legal framework, general government policies and public health policy objectives. This also includes any treaties, conventions and regional or international agreements to which the country is a party as well as any supranational legislation having an effect on constituent Member States.

Overlap and conflicts with existing laws and regulations should be avoided since this causes confusion and the duplication of mandates, unnecessary regulatory burden and the likelihood of noncompliance. Manufacturers, importers, distributors and other stakeholders should be able to consistently identify which authority is responsible for what.

This is especially important where the regulation of medical products is decentralized – when, for instance, there may be central and state/provincial-level authorities. Effective systems of mutual consultation, cooperation and coordination between the different levels of government should be put in place in order to promote the national uniformity of regulatory requirements while respecting local responsibilities. It is essential that all the different regulatory functions and activities are efficiently integrated allowing for the uniformity of the regulatory system.

The same considerations are equally important when more than one institution or department within the same level of government is responsible for different, or the same, regulatory functions and products – a situation which is not uncommon. The problems associated with unclear or conflicting mandates and requirements can and do result from complex regulatory systems, compounded by challenges in effective communication and coordination.
In all instances, formal mechanisms should be established to ensure proper coordination during the drafting and execution of the regulatory instruments and the ongoing operations of bodies charged with the regulatory oversight of medical products.

Consistency in regulatory actions and decisions means that the same or similar circumstances should lead to the same or similar outcomes. It is therefore important for the regulatory system to build an institutional memory to keep records of decisions made in order to offer similar and fair treatment to future similar situations. Consistency is supported when the regulatory framework provides for appealing regulatory decisions through an impartial appeals process. The enforcement of such, and corrective measures, should also be consistent across sectors.

Consistency is also supported by having sufficient and clear regulatory guidance based, whenever possible, on international guidelines; the orientation and training programmes for staff; and regular discussions with regulated parties and other key stakeholders that serve as mechanisms for the identification and resolution of issues.

The application of a well-functioning quality management system that spans all regulatory activities (24) is critical for achieving regulatory consistency. This includes, among others, the adoption of a process approach involving the systematic definition and management of regulatory processes, and their interactions, so as to achieve the intended results in accordance with the quality policy and strategic direction of the organization.

Performance based indicators, internal reviews and external audits can also play an important role in ensuring consistency in the application of regulations and regulatory operations.

### 8.3 Independence

Institutions executing regulatory oversight of medical products should be independent.

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<th>Key elements:</th>
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<tr>
<td>• The regulatory system must operate, and be seen to operate, in an independent and authoritative manner, discharging its duties independently from politicians, government and regulated entities.</td>
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<tr>
<td>• Regulatory activities and decisions should avoid improper and undue influence from stakeholders (also known as regulatory capture).</td>
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<tr>
<td>• The appropriate funding and clarity on funding processes is essential.</td>
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<tr>
<td>• Independence of leadership should be put in place in order to support independent behaviour while in employment and upon exiting.</td>
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According to an OECD publication entitled *Creating a culture of independence* (20), "regulatory agencies (authorities) often find themselves under various pressures from different stakeholders and interest groups which can subject them to different forms of influence. To ensure they conduct their activities correctly and achieve the right policy outcomes they must take on board legitimate interests and protect themselves from inappropriate or undue influence".

Good governance and anti-corruption measures (16) should be built into the regulatory framework to avoid actual or perceived conflicts of interest, unfounded bias or improper influence by stakeholders (also known as regulatory capture). To maintain public confidence, the regulatory authority must operate, and be seen to operate, in an independent, authoritative and impartial manner, discharging its duties independently of those regulated entities (e.g. independence from researchers and industries).

For regulators that are funded through fees, an appropriate cost-recovery mechanism is essential to set the “right” fee and avoid a regulator that is under-funded, captured by industry or undermined by the executive. It can be easier to influence a regulator funded through general government revenues by reducing the resources at its disposal. Annual appropriations can make it easier to influence the regulator than multi annual appropriations that are less susceptible to short-term shocks, such as political/electoral imperatives. Adequate safeguards can protect the budget process from being used to unduly direct the regulator.

The nomination and appointment of the regulator’s leadership should be based on transparent and accountable processes. Clear conflict of interest rules should be in place to support independent behaviour while in employment and upon exiting.

### 8.4 Impartiality
All regulated parties should be treated equitably, fairly and free from bias.

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<th>Key elements:</th>
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<tr>
<td>• Regulatory activities and decisions should avoid conflicts of interest or unfounded bias.</td>
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<tr>
<td>• The regulatory system must operate in an impartial manner.</td>
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<tr>
<td>• The regulatory authority should not be engaged in activities it regulates nor be at a hierarchal level that is subordinate to institutions that perform regulated activities.</td>
</tr>
<tr>
<td>• Regulatory decision should be science- and evidence-based and the decision-making process should be robust, according to defined criteria.</td>
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Regulatory instruments must be written so that regulatory activities and decisions made on the basis of such instruments are legitimate, evidence-based and ethical. Public and private bodies, domestic and foreign entities should all be regulated equitably using the same principles and framework so that *competitive neutrality* is achieved.

The regulatory authority must operate in an impartial manner, discharging its duties independently of those regulated entities (see 9.3 *Independence*).

This principle also extends to researchers and other experts sitting on scientific and advisory committees convened to provide recommendations to the regulatory authority on matters related to regulatory policy or the authorisation of medical products. Declarations of interest have to be completed and reviewed, and rules for withdrawal need to be defined prior to discussions to maintain the integrity and impartiality of the committee and its recommendations.

Furthermore, the regulatory authority should not be engaged in the activities it regulates nor be at a hierarchal level that is subordinate to those institutions that perform regulated activities, including the procurement of medical products by a ministry of health or other government institution.

Regulators can avoid actual or perceived influence by being open and transparent about their decisions and decision-making process. This will help ensure impartiality, better regulatory outcomes and increased public confidence in the use of the regulated products.

Regulatory activities and decisions should be science-driven, evidence-based and predictable. While there will always be a need for good regulatory judgement and discretion in enforcement, actions and decisions should be based on regulatory requirements and on the evidence or circumstances of the situation (also supports 9.2 *Consistency*).

### 8.5 Proportionality

Regulatory oversight and regulatory decisions should be proportional to risk and the regulator’s capacity to implement and enforce.

<table>
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<th>Key elements:</th>
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<tr>
<td>• Regulatory oversight should be adequate to achieve the objectives without being excessive.</td>
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<tr>
<td>• Regulatory measures should be proportionate to the risk of the product or activity or service.</td>
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<tr>
<td>• Regulation should not exceed the national capacity to implement and enforce the regulation.</td>
</tr>
<tr>
<td>• The assessment of medical products should be based on a benefit/risk evaluation and continuous monitoring of the benefit/risk profile through a robust vigilance system.</td>
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The principle of proportionality means that an action does not go beyond what is needed to achieve an intended objective. This principle should be applied to all elements of a regulatory system. Regulation should be created only when necessary and should be adequate to the aim being pursued without being excessive. The content and form of regulation should be appropriate to both the issue being addressed and the risk it poses. For instance, extensive pre-clinical and clinical studies are needed to support the safety and efficacy for the marketing authorization of a new medicine, whereas, limited safety/efficacy studies, usually in a form of a single in vivo bioequivalence study or, where appropriate, in vitro studies, are sufficient for generic medicines.

Regulatory enforcement and inspection regimes should also be proportionate to the risk and severity of the infraction with an aim to reduce or mitigate the health risk posed by the infraction. A proportionate, risk-based approach allows the regulator to allocate resources where the need is greater. It also ensures that the cost of complying with regulation is proportionate to the nature of the risk.

The principle of proportionality also applies to the policies and processes by which regulation is made. The regulation-making process should be flexible and proportionate to the complexity and/or impact of the problem that it addresses. For instance, a rigorous cost/impact analysis may be required for a new complex regulatory framework but not for simple regulations or where the policy alternatives are limited. Regulation should not exceed national capacity to implement and enforce the regulation. “If there are no strategies, facilities and resources for implementation and enforcement, legislation on its own will achieve nothing. A law with modest aims and objectives that is properly enforced is preferable to a more comprehensive one that cannot be implemented”(12). Furthermore, the lack of resources or ability to implement and enforce represents a liability for the government.

The assessment of medical products should be based on a benefit/risk evaluation. All the demonstrated benefits from the medical products should be weighed against the identified risks in order to determine if the benefit outweighs the risks. Regulatory systems should have appropriate vigilance processes in place in order to monitor the benefit/risk profile and to take any regulatory actions if required.
8.6 Flexibility

Regulatory oversight should allow for flexibility in responding to a changing environment and unforeseen circumstances.

Key elements:

- The regulatory system, including regulatory frameworks, should provide sufficient flexibility to reflect/respond to changes in the regulated environment, including evolving science and technology.
- The regulatory system should be prepared and provide for timely response to urgent situations, including public health emergencies and shortages of medical products.
- The language of regulation should be performance-based whenever possible, allowing for alternative approaches that achieve the same result.
- The regulatory system should provide the flexibility to apply good judgement.

Flexibility is essential to ensure that regulatory frameworks and regulatory systems remain “fit for purpose”. This requires the appropriate design and use of regulatory instruments.

In developing a meaningful, understandable and enforceable regulatory framework, there is a need to provide sufficient detail to ensure clarity. At the same time, the regulatory framework should allow flexibility to respond to new technologies and innovation, to changes in the regulated environment and to enable a timely response to unforeseen public health threats. It should provide for the regulator’s administrative and enforcement discretion – that is, the flexibility to apply good judgement within the regulatory framework. This discretion must be subject to the appropriate controls and oversight. Flexibility in regulatory oversight should also be risk-based and must not compromise the ability to ensure the quality, safety and efficacy and performance of the product (19).

Responsiveness is an extended principle of flexibility, however slightly different. Responsiveness is time-bound and temporary in nature due to the fact that it addresses urgent situations such as public health emergencies, serious shortages of medical products with no alternatives, unmet medical needs and rare disorders, and the use for compassionate and donation purposes. Regulatory systems should be well prepared and equipped with the necessary regulatory instruments to respond to and manage these unforeseen situations. Flexible and responsive provisions are critical for providing the authority with the ability to make decisions based on best available science and benefit/risk considerations, often in the face of less-than-complete information (e.g. compassionate use, emergency use authorization or listing). The lack of necessary regulatory tools and the flexibilities they afford can pose real and significant impediments to public safety, particularly in times of public health emergencies.
During times when regulatory responsiveness is urged, a regulatory authority should consider the prioritization of its activities using a risk-based approach. The involvement of policy and decision-makers, as well as regulatory collaboration and coordination within the international regulatory community, significantly contributes to regulatory responsiveness.

Flexibility and responsiveness within regulatory framework should aim to accommodate continuing evolution in science and technology. The language of the regulations that support the law should normally be performance-based rather than prescriptive (6), thus allowing regulated parties to use alternative approaches that achieve the same outcome.

Guidelines and other guidance documents are the most detailed, most flexible and most amendable of the regulatory framework instruments. These attributes allow the regulatory framework to respond to new risks in a timely manner and allow for the possibility that an unforeseen technology may be used in a future medical product. Unlike laws and regulations, guidelines in themselves usually do not have the force of law. However, guidelines are very effective if appropriately anchored to the regulation and used to describe how compliance with the regulation may be achieved. They should also allow for other scientifically justified approaches to compliance. Alternate approaches to the principles and practices described in a guidance may be acceptable provided they are supported by adequate scientific justification. The flexibility and amendable attributes that guidelines offer is lost if such detailed texts are put into regulation.

In circumstances where science is rapidly evolving and not sufficiently mature to justify the development of regulatory guidelines, ‘points to consider’ type documents can provide useful principles-based guidance and definitions that promote best practices, a common regulatory understanding, international convergence, and prepare the ground for eventual guidelines. Existing international guidelines and standards should always be considered when new guidance documents are being developed.

The regulation of medical products is complex and ever-evolving. New technologies and practices will continue to pose challenges to regulatory systems and redefine the boundaries of what can and should be regulated. Prior to the possible development of regulations designed to deal with new technologies or address certain practices, regulators will often need to generate the necessary regulatory flexibility through the appropriate interpretation of existing legislation and regulations.
### 8.7 Clarity
Regulatory requirements should be accessible to and understood by users.

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<th>Key elements:</th>
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<tr>
<td>• Regulatory instruments should be written in language that is understood by users.</td>
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<tr>
<td>• Terminology should be defined and consistent with international norms whenever possible.</td>
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<tr>
<td>• Consultation, education and training on new requirements contribute to clarity and compliance.</td>
</tr>
<tr>
<td>• Guidelines and <em>good guidance practices</em> are instrumental to proper interpretation of regulations.</td>
</tr>
<tr>
<td>• The process and basis for taking regulatory decisions and enforcement actions should be clear.</td>
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The compliance with and consistent application of regulatory requirements and processes require a clear understanding of what is expected. Both the regulator and the regulated party should understand the conduct that is expected and the consequences of non-compliance.

Proposed regulatory instruments should be written in language that can be understood by intended users. This will require the collaboration of regulatory programme personnel and legal drafters, taking into consideration the objectives of the legal instrument, the intended audience and other potentially impacted stakeholders, as well as feedback from internal and external consultations. Clear, unambiguous and precise instruments that are drafted in a language and form consistent with other laws and regulations reduce the potential for disputes or misinterpretation and also promote compliance.

As an initial step in the process, the authority drafting medical product regulations should conduct a review to identify areas that lack clarity and resolve any inconsistencies – whether within the regulation itself or between regulations. This also serves as an opportunity to review the “regulatory stock” – the accumulated body of applicable regulations – to identify the need for future updating and better integration of regulatory requirements with a view to eliminating inconsistencies, redundancies and complexity or adapting to new requirements.

Providing interested parties, including the public, the opportunity to be informed of and contribute to the process of regulatory development and regulatory impact analysis is critical to improving the quality and language of the regulatory instrument, promoting a clear understanding of what is intended, and increasing the likelihood of buy-in and future compliance. The means by which interested parties can contribute should be made clear.
Regulatory impact analysis is a valuable tool for systematic assessment of the expected effects of regulatory proposals. It is usually undertaken by the policy analysts of the regulatory departments, agencies or ministries that sponsor the proposal and is primarily aimed at assisting decision-makers in their consideration of a recommended proposal. The product of the regulatory impact analysis process is a document that summarizes the regulatory proposal, the potential alternatives and the implementation aspects and impacts of the proposal.

Terminology should be defined whenever possible to avoid ambiguity or misinterpretation. Where possible, terminology should be consistent with established international norms, standards and harmonized guidelines. As noted, international standards and guidelines are particularly important as vehicles to promote a common regulatory language, convergence and international cooperation.

The principle of clarity is equally important and applicable to the development of regulatory and administrative guidelines which are instrumental in interpreting and providing operational clarity to regulations. Guideline development should follow good guidance practice to ensure that guidelines are written in a clear and concise manner and are consistent with other guidelines and the underlying regulations. This includes the use of standard templates and formats, writing style guides, editors, and experts with a good knowledge of the regulatory framework.

Draft guidelines, as with regulations, should be subject to internal and external consultation. Consultation will help confirm if language is clear or if it requires some refinement to improve comprehension. Plain language and simple sentence structure should be the goal as well as to give illustrative examples where possible.

Education, awareness sessions and training, along with clear timelines for the adoption of new regulations and guidelines, should also be considered as tools to promote clarity and compliance when introducing or amending regulations and guidelines, particularly when complex in nature.

Regulations and supporting guidelines should be reviewed periodically to ensure that they still reflect the authority’s current practices and expectations, are adapted to the scientific and technological developments, and are aligned with current international standards and guidelines, where applicable. When reviewing and revising any guideline, one must consider the consequential changes in other existing guidelines that will need simultaneous revision.

From an operational perspective, the process and basis for taking regulatory decisions and enforcement actions should be clear and accessible to those directly impacted or otherwise affected (see 7.9 Transparency).
In summary, clarity is essential in all aspects of regulatory oversight (requirements, procedures, decisions and communications) if regulatory programmes are to have the desired effect.

### 8.8 Efficiency

Regulatory systems should achieve the intended results within the required time and at reasonable effort and cost.

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<tr>
<td>Efficient regulatory oversight are those that achieve the intended public health goals.</td>
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<tr>
<td>A sound regulatory framework, competent staff and the effective use of resources and information from other authorities are the key elements of an efficient regulatory system.</td>
</tr>
<tr>
<td>Policy-makers should seek the most efficient and least burdensome means of achieving their regulatory purposes and confirm actual effectiveness once implemented.</td>
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<tr>
<td>In considering a regulatory approach, the total burden and resource needs of cumulative regulation should be evaluated.</td>
</tr>
<tr>
<td>Regulatory authorities should continually explore ways of improving efficiency in fulfilling their mandate.</td>
</tr>
<tr>
<td>Alignment of regulatory requirements with other countries and international collaboration promote efficiency.</td>
</tr>
<tr>
<td>Regulated entities play a critical role in contributing to the efficiency of regulatory systems.</td>
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<tr>
<td>The efficiency of regulatory instruments and regulatory operations should be assessed using performance-based indicators.</td>
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An efficient regulatory system must be science- and evidence-based, apply the principles of risk assessment and management, and embed a strategy of international regulatory cooperation into daily business. A regulatory system that is unable to make sound decisions in a timely and consistent fashion is not effective. This is not only a matter of having sufficient resources but also having the right resources and using them effectively, irrespective of size. In this context, lack of integrity of the overall regulatory system is a barrier to regulatory efficiency.

Less resourced regulatory systems can be as effective as more resourced systems if risk-based and if advantage is taken of the work and decisions of other regulatory authorities while focusing resources on essential, value-added activities which only the regulatory authority is in a position to perform (17).
Regulatory oversight cannot be considered efficient if it creates unjustified barriers to access, trade and international regulatory cooperation. The successful establishment of effective regulatory controls on medical products depends on a number of factors as previously described, including:

- The analysis of options that includes the results of consultation with stakeholders. Regulations are more likely to be effective if those impacted have provided input.
- Regulations that are proportional to perceived risk.
- Early-stage planning for implementation and the practicalities of future enforcement. Application and enforcement should not be after-thoughts.

When new regulatory instruments are being developed and subjected to regulatory impact analysis, the regulatory authority should develop “strategies for education, assistance, persuasion, promotion, economic incentives, monitoring, enforcement, and sanctions” (24). The authority must decide which compliance strategies will be established and whether or not consumer awareness and market forces can reasonably be used, in addition to the threat of penalties. The role of civil society in monitoring adherence to regulation should also be considered, if appropriate.

Co-regulation may also be considered in certain circumstances. In such situations, a government would issue regulations and enter into a non-statutory agreement with a body to develop and administer a compliance program. While a government works with and through the body in regulating the activity, it has not delegated its oversight of the activity.

The use of third parties can also be considered by regulatory authority to conduct their activities, a model prevalent in the regulation of medical devices; for example, the use of recognized auditing organizations to conduct audits of manufacturers’ quality management systems to an international standard and applicable regulatory requirements. Regulatory resources are directed at establishing and maintaining oversight of audit organizations, providing more effective use of limited regulatory resources (25).

A government incurs costs by establishing and maintaining regulatory systems. Industry and other regulated parties incur costs in complying with regulation; for example, in undertaking studies, preparing application dossiers, maintaining records and paying fees – the cost of doing business.
Additional costs accrue from inefficient regulatory systems. If the cost of complying with regulation is disproportionately high, companies may decide against placing products on the market. For instance, a mandatory requirement to conduct local clinical trials as a condition for marketing authorisation could be a disincentive to enter a market, especially if trials conducted elsewhere reflect the patient profiles of the intended market and demonstrate safety and efficacy of the product. Similarly, lengthy product review times translate into lost revenue and unnecessary delays in the availability of products for patients – with potentially significant negative implications in terms of morbidity/mortality, health care costs and the economy (healthy economies require healthy people).

Inefficiency also costs regulatory authorities in terms of sub-optimal impact for available resources, reputation, job satisfaction and time spent addressing complaints related to performance. Regulatory frameworks reflecting the principles of proportionality, flexibility and consistency are more likely to be effective. They allow for resources to be allocated to the regulatory activities where they are most needed.

**International collaboration.** Regulatory frameworks that are consistent and aligned with those of other countries and regions encourage the investment needed to bring appropriate and affordable products to that market. Internationally consistent frameworks also enable the regulatory authority to participate in work-sharing networks and other forms of regulatory cooperation (including convergence, harmonization, information- and work-sharing, reliance and recognition). When properly anchored in the regulatory framework, reliance on the work of other authorities eliminates or reduces the inefficient duplication of regulatory evaluations of medical products and the inspection/audit of facilities.

Regulatory authorities should continually explore the means of improving efficiency while maintaining standards for evaluating the quality, safety and efficacy/performance of medical products. For example, this could include the introduction or refinement good review practices (18) and a quality management system (19); greater and more effective use of information technology; consultations with industry on common deficiencies and how best to address them; risk-based criteria for scheduling and conducting inspections; addressing gaps in guidance; performance measurement; and – as highlighted above – regulatory cooperation and reliance.

Industry also plays a critical role in contributing to the efficiency of regulatory systems. As an example, high quality applications for marketing authorization reduce the overall review time by reducing the number of deficiencies and review cycles. Similarly, a manufacturer with a good compliance record should not require the same frequency and depth of inspection as a poorly performing manufacturer. Consultations and training can be effective complements to enforcement actions in achieving the desired level of compliance.
As part of the regulatory impact analysis process, policy-makers should seek the most efficient and least burdensome means of achieving their regulatory purposes at a minimum reasonable cost, including non-regulatory options. In considering a regulatory approach, there should be consideration of the total burden and resource needs of cumulative regulation.

Periodic performance assessments should evaluate the actual efficiency of regulatory instruments that are implemented in order to ensure that the foreseen benefits have been achieved and, if so, what the direct and indirect costs are.

### 8.9 Transparency

Transparency is the hallmark of a well-functioning regulatory system and essential to building public trust and enabling international cooperation.

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<tr>
<td>• Transparency requires investment and a culture of openness, supported by government policy, commitment and action.</td>
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<tr>
<td>• The process of developing new or revising existing regulatory instruments should include stakeholder consultation.</td>
</tr>
<tr>
<td>• Regulatory requirements, processes, fees, assessments, decisions and actions should be accessible as much as possible.</td>
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<tr>
<td>• The regulatory authority’s disclosure policies should be consistent with national laws on access to information.</td>
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"Informed opinion and active co-operation on the part of the public are of the utmost importance in the improvement of the health of the people." - World Health Organization Constitution

Transparency is a hallmark of a well-functioning regulatory system. It is in the interests of patients, consumers, governments, health care workers and manufacturers as it increases the level of public trust and confidence in the regulatory oversight of medical products. Transparency in regulatory requirements and actions allows for better-informed investment decisions in the public and private sectors and discourages discriminatory, corrupt or abusive practices.

Transparency means that all affected and potentially interested parties – domestic, foreign, public and private – have meaningful opportunities to be informed of new or amended regulations and guidelines and to make their views known before they are enacted.
Transparency means that, once adopted, medical product regulations and guidelines are readily available and accessible to stakeholders and the general public. Relevant laws, regulations and guideline documents should be posted on the authority’s website. Additionally, national industry and professional associations will often work with regulatory authorities to disseminate new regulatory texts or to provide opportunities for the exchange of relevant information.

The assessments, decisions (positive and also, when possible, negative ones) and actions of the regulatory authority should be documented and made publicly available. Such information is important to a broad range of stakeholders - including industry, researchers, health professionals, patients and consumers - who will use the information for a variety of purposes. It is also an essential element to building trust and confidence in the regulatory system.

Regulated parties should be able to access the full product assessment or site inspection reports that pertain to them. In addition to providing an insight into the basis for comments and decisions, it also serves as an educational tool that can help improve regulatory compliance and the quality of future submissions. This practice can also be beneficial to the regulatory authority by fostering a culture of transparency and accountability at the operational and management level. Furthermore, it can lead to higher quality reports by ensuring that reports clearly explain how such assessments led to decisions.

Transparency requires investment and a culture of openness that, in turn, must be supported by government policy, commitment and action. While it may not be possible for all regulatory authorities to implement the full range of measures that define an optimally transparent regulatory system, a step-wise approach can be adopted. Given the prevalence of smart devices and the internet, efforts could be directed towards establishing and maintaining an up-to-date, searchable public website that contains certain basic information, including:

- Information on the regulatory authority – roles, responsibilities, organization, and contact information.
- Access to laws, regulations, guidelines and procedures necessary to satisfy regulatory requirements and improve the safety and quality of medical products.
- A searchable product registry of approved, suspended and withdrawn products.
- Product information for health care professionals and patients.
- Licensing status of manufacturing sites.
- Health advisories, safety information, quality or substandard and falsified medical product alerts, recalls and other time-sensitive information of public health interest.
- Performance targets/results and annual reports.
- Proposed new regulatory instruments, including comment periods and how to provide input.
The findings of all audits or oversight reviews of the performance and functioning of the regulatory authority should be made public. Such reviews are an important element of public accountability, as is the establishment and ongoing reporting of performance against regulatory targets and the publication of annual reports.

As it fulfils its responsibilities, the regulatory authority will necessarily create or come into possession of proprietary or confidential information. Examples include personal identifiable information from clinical trials or reports of adverse events, specifications of medical product compounds or materials, and key manufacturing processes. Measures should be established to prevent the inappropriate disclosure of such specific information. There should be a mechanism to address instances when the proprietary nature or confidentiality of the information is in dispute.

In general, national law and regulation should favour transparency and public access in both the process and the criteria of regulatory decision-making. The regulatory authority’s disclosure policies should be consistent with the national laws on public access to government information or “freedom of information”. Procedures and contact points to obtain information held by the regulatory authority should be accessible and clear.

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations. It is incumbent upon regulators to practice transparency in regulatory operations and decisions as a fundamental principle of GRP but also towards building trust and maximizing opportunities for cooperation and reliance as part of a shared regulatory community responsibility.

9. Enablers for good regulatory practices

An enabling environment will facilitate a successful implementation of GRP. The non-exhaustive list of GRP key enablers include:

9.1 Political and government-wide support

A sustained support at the highest political and government levels, including policy makers, is essential for the proper implementation of the concept and principles of GRP.

GRP should form an integral part of government-wide policies on regulatory system and, in addition, be backed by strong political support.
9.2 Effective organization and good governance supported with leadership

The structure and line of authority among and within all institutions of the regulatory system should be well defined. The integrity of the overall regulatory system is critical to the effective and efficient performance of all institutions composing the regulatory system. If more than one institution is involved in the regulatory system, the legislation or institutional regulation should provide for clear coordination and avoid an overlap of the regulatory activities. Leadership is critical for setting and carrying out the organizational vision, mission, policies and strategies which in turn significantly contribute to organizational efficiency.

9.3 Inter-and-intra-organizational communication, collaboration and coordination

Adequate and effective communication plays a fundamental role for exchanging information within and outside the institutions forming the regulatory system. When regularly communicating both internally and externally, regulatory authorities remain more transparent and accountable. Communicating correct information prevents the potential misunderstandings and dissemination of misleading information to patients and the public. Communication is a powerful tool for collaboration and coordination with relevant stakeholders at national and international levels which in turn feed into an effective and efficient use of resources and better regulatory outcomes.

9.4 A robust and well-functioning quality management system

QMS (19), which includes the application of quality risk management (QRM) principles, is a valuable tool that helps regulatory authorities to achieve greater credibility for their decisions, and greater stability and consistency in their operations. QMS contributes to systematic planning, control and improved quality in all processes throughout all regulatory functions and ensures a comprehensive approach for all.

9.5 Sufficient and sustainable financial resources

Investment in regulatory systems is critical to a well-functioning health care system. Securing financial resources to effectively carry out the regulatory mandate and to continuously improve the performance of regulatory activities is an essential enabler for regulatory system independence, impartiality, consistency and efficiency. The financial resources of all institutions of the regulatory system should be sustainable, apart from donors’ or philanthropic entities donations.
9.6 Competent human resources

An array of knowledge and the skills of regulatory staff contribute to the development, implementation and maintenance of a regulatory system for medical products. Personal and career development policies and measures (e.g. training programmes, competitive remuneration schemes) are critical for regulatory authorities to attract and recruit competent staff and, in addition, to retain staff in the service.

9.7 Pre-set organizational ethics and values

Regulatory activities should abide by ethical principles, organizational values, and professionalism. All regulatory staff should be made aware and be trained on the ethics and values as set by the regulator authorities (e.g. code of conduct). A system should be established, within or external to the regulatory system, to manage situations of departure from the organizational ethics and values.

9.8 Science- and data-driven decision-making process

Regulatory decisions, along with their making process, should be based on scientific foundations and accurate data rather than intuitions or arbitrariness. Science-based decisions provide for the consistency and predictability of regulatory outcomes.

The above-listed enablers do not work in a stand-alone mode. Rather, they work in harmony to realize the application and implementation of GRP; for example, the sufficient and sustainable financial resources contribute to the recruitment, development and maintenance of competent human resources. Similarly, financial resources shall be managed following good governance practices.

10. Implementing good regulatory practices

WHO Member States are encouraged to implement GRP in their regulatory systems with due consideration to their legal and regulatory system realities. Transparent and predictable processes should aim to develop high-quality regulatory oversight that achieves intended objectives while also minimizing negative impact and costs.

At the same time, there should be sufficient flexibility to allow the processes to be applied proportionately to the scope, magnitude and complexity of the issue. Sustained support at the highest levels, along with adequate resourcing, is essential.

Further guidance will be developed to assist Member States both in establishing new regulatory systems for medical products and in updating existing ones.
11. Acknowledgements

WHO wishes to acknowledge all the authors, stakeholders and organizations who contributed to the preparation of this document.

12. Glossary

The definitions given below apply to the terms as used in this document. They may have different meanings in other contexts. Readers are also encouraged to consult related WHO guidances for a more complete set of definitions relevant to best regulatory practices (see References).

**public health emergency.** A public health emergency (the condition that requires a governor to declare a state of public health emergency) is defined as "an occurrence or imminent threat of an illness or health condition, caused by bioterrorism, epidemic or pandemic disease, or (a) novel and highly fatal infectious agent or biological toxin that poses a substantial risk of a significant number of human facilities or incidents or permanent or long-term disability (WHO/DCD, 2001). The declaration of a state of public health emergency permits a governor to suspend state regulations and change the functions of state agencies (26).

**quality management system (QMS).** An appropriate infrastructure encompassing the organizational structure, procedures, processes and resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

**recognition.** The acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority is sufficient to meet the regulatory requirements of the relying authority.

**regulatory convergence.** A voluntary process whereby the regulatory requirements in different countries or regions become more similar or “aligned” over time. The process results from the gradual adoption of internationally recognized technical guideline documents, standards and scientific principles, common or similar practices and procedures, or the establishment of appropriate domestic regulatory mechanisms that align with shared principles to achieve a common public health goal (27).
**regulatory cooperation.** A practice between regulatory authorities aimed at the efficient and effective regulation of medical products. Regulatory cooperation can be practised by an agency or institution or on a government-wide basis. The range of formal mechanisms include the creation of joint institutions and treaties and conventions such as mutual recognition agreements, while less formal practices include the sharing of information, scientific collaboration, common risk assessment, joint reviews and inspections and the development of standards. Regulatory cooperation may also include work with international counterparts to build regulatory capacity or provide technical assistance, thus contributing to the improvement of international regulatory governance practices (28) (29) (30) (31).

**regulatory harmonization.** The process whereby technical guidelines are developed in order to be uniform across participating authorities in multiple countries (32).

**regulatory impact analysis.** The process of examining the likely impacts of a proposed regulation and alternative policy options to assist the policy development process (33).

**regulatory stock.** The collection or inventory of accumulated regulations.

**regulatory system.** The combination of institutions, processes and the regulatory framework through which a government controls the particular aspects of an activity (34).

**reliance.** The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.
13. References


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3.6 TEST FOR HISTAMINE-LIKE SUBSTANCES
(VASODEPRESSOR SUBSTANCES)

Draft proposal for revision in *The International Pharmacopoeia*

**DRAFT FOR COMMENTS**

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int) by 18 September 2020.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

【Note from the Secretariat.】Comments are sought on the proposal to suppress chapter 3.6 Test for histamine-like substances (vasodepressor substances) in *The International Pharmacopoeia* and the references to this chapter in the monographs on Bleomycin sulfate, Spectinomycin hydrochloride, Streptomycin sulfate. The proposals follows the strategy to phase-out animal testings where possible and justified.

The test for vasodepressor substances is carried out in cats by comparing the depression of arterial pressure caused by the test solution with that obtained after administration of a solution of histamine. Changes from the current chapter are indicated in the text by insert or delete.】
3.6 TEST FOR HISTAMINE-LIKE SUBSTANCES (VASODEPRESSOR SUBSTANCES)

3.6 Test for histamine-like substances (vasodepressor substances)
The test for vasodepressor substances is carried out in cats by comparing the depression of arterial pressure caused by the test solution with that obtained after administration of a solution of histamine.

Recommended procedures
Use healthy, adult cats, either males or non-pregnant females.

Determine the weight of the animal and place under general anaesthesia by injection of chloralose R or a suitable barbiturate that allows the maintenance of uniform blood pressure. Protect the animal from loss of body heat and maintain it so that the rectal temperature remains within physiological limits. Introduce a tube into the trachea. Surgically expose the common carotid artery and by blunt dissection separate it completely from all surrounding structures, including the vagus nerve. Insert a cannula filled with heparinized saline TS into the artery and connect it to a mercury manometer or another suitable device arranged for making a continuous record of blood pressure. Surgically expose the jugular or the femoral vein and insert into it another cannula filled with heparinized saline TS through which can be injected solutions of histamine and of the test substance.

Determine the sensitivity of the animal to histamine in the following way: Start the recording kymograph or a similar recording device and inspect the tracings for amplitude of excursion and relative stability of blood pressure. Inject into the jugular or femoral vein histamine TS, in doses of 0.05 μg (dose A), 0.1 μg (dose B) — repeated at least 3 times — and 0.15 μg (dose C) of histamine base per kg of animal weight. Administer the second and subsequent injections not less than 1 minute after the blood pressure has returned to the level recorded immediately before the previous injection. Repeat this series of injections until, disregarding the first series of readings, a relatively uniform decrease in blood pressure is obtained after doses B of histamine. The animal should be used for the test only if the decrease after doses B is not less than 2.7 kPa (20 mm Hg) and, moreover, if dose A causes smaller responses than doses B whereas dose C gives greater responses than doses B.

Prepare the test solution as described in the monograph. During the course of the test, take care to maintain a uniform rate of injection for both the test solution and the standard solution. If the jugular vein is used, care should also be taken that the injection of test solution and histamine standard are given in equal volumes to avoid volume effects on blood pressure. When a common cannula is used for both the standard and test solutions, each injection of the standard and test solution should be immediately followed by an injection of approximately 2.0 mL of saline TS to flush any residues from the tubing.
Inject a dose B of the standard solution followed by an injection of the specified amount of the test solution and then another dose B of the standard solution. The second and third injections are given not less than 1 minute after the blood pressure has returned to the level recorded immediately before the preceding injection. If the response to the test solution is greater than that given previously by dose A, repeat the series of injections twice and conclude the test by giving dose C of standard solution. If the response to dose C is not greater than that to dose B, the test is invalid.

The animal may be used in the test as long as it remains reasonably stable and responsive to histamine and provided that (a) an injection of test substance did not cause a greater depressor response than that caused by dose C and (b) the response to dose C of the standard solution given after the administration of the test substance does not become lower than the mean response to doses of B previously injected.

The substance passes the test if the response or the mean of the responses after the injection of the amount specified in the monograph is smaller than the mean of the corresponding responses to dose B of the standard solution (0.1 μg of histamine base per kg of animal weight), and no one single dose of the test solution causes a greater depressor response than dose C of the standard solution (0.15 μg of histamine base per kg of animal weight).

Reference to 3.6 Test for histamine-like substances in monographs:

Bleomycin sulfate (Bleomycinii sulfas)

Manufacture. The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

Histamine-like substances. Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using 1 mL per kg of body mass of a solution in saline TS containing a quantity equivalent to 500 IU per mL.

Spectinomycin hydrochloride (Spectinomycini hydrochloridum)

Histamine-like substances. Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using 1 mL per kg of body mass of a solution in saline TS containing 25 mg of the substance to be examined per mL.

Streptomycin sulfate (Streptomycinii sulfas)

Manufacture. The method of manufacture is validated to demonstrate that the product, if tested, would comply with the following test.

Histamine-like substances. Carry out the test as described under 3.6 Test for histamine-like substances (vasodepressor substances) using, per kg of body weight, a solution containing 3 mg of streptomycin base in 1 mL of saline TS.
ALBENDAZOLE CHEWABLE TABLETS
(ALBENDAZOLI COMPRESSI MANDUCABILI)

Draft proposal for revision for *The International Pharmacopoeia*

**DRAFT FOR COMMENTS**

Please send any comments you may have on this draft working document to **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (email: schmidt@who.int) by **30 September 2020**.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

*Note from the Secretariat.* It is proposed to revise the Dissolution test in monograph on Albendazole chewable tablets based on information received by a manufacturer. Comments are invited on the revised section.

Manufacturers of Albendazole chewable tablets and Albendazole tablets are invited to submit samples of their products so that the applicability of the revised dissolution procedure for their product(s) can be tested.

For further information regarding the submission of samples, please contact Dr Herbert Schmidt at schmidt@who.int.

Changes from the current monograph are indicated in the text by insert or delete.
ALBENDAZOLE CHEWABLE TABLETS  
(ALBENDAZOLI COMPRESSI MANDUCABILI)

Category. Anthelminthic.

Storage. Albendazole chewable tablets should be kept in a tightly closed container.

Labelling. The designation on the container should state that the tablets may be chewed, swallowed whole or crushed and mixed with food or liquid, and that the tablets should be crushed before being given to a young child.

Additional information. Strengths in the current WHO Model List of Essential Medicines (EML): 400 mg. Strengths in the current EML for children: 400 mg.

Requirements
Comply with the monograph for Tablets.

Definition. Albendazole chewable tablets contain Albendazole in a suitable basis that may contain suitable flavouring agents. They contain not less than 90.0% and not more than 110.0% of the amount of Albendazole (C₁₂H₁₅N₃O₂S) stated on the label.

Identity tests
• Any two of tests A, B and C may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using the chromatographic conditions given under “Related substances”, Test B. Apply separately to the plate 10 µL each of the following solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of glacial acetic acid R. For solution (A), shake a quantity of the powdered tablets containing about 2.5 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B), use 0.1 mg of albendazole RS per mL. For solution (C), use 0.1 mg of albendazole RS and 0.1 mg of oxibendazole R per mL. After removing the plate from the chromatographic chamber, allow the plate to dry in a current of warm air and examine the chromatogram under ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.
   The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

B. See the test described below under “Assay”, Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to the retention time of the peak due to albendazole obtained with solution (3).
C. See the test described under “Assay”, Method B. The absorption spectrum (1.6) of the test solution, when observed between 220 and 340 nm, exhibits maxima at about 231 nm and at 308 nm; the absorbance at 308 nm is about 0.59.

**Dissolution**

*For 200 mg tablets*: carry out the test as described under 5.5 **Dissolution test for solid oral dosage forms** using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes, withdraw a sample of about 10 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature and dilute 2.0 mL of the obtained solution to 25.0 mL with the dissolution medium. Use this solution as solution (1). For solution (2), dissolve 44.0 mg of albendazole RS in 10.0 mL of sulfuric acid/methanol (1%) TS and immediately dilute to 100.0 mL with of hydrochloric acid (~3.65 g/L) TS. Dilute 2.0 mL of this solution to 50.0 mL with hydrochloric acid (~3.65 g/L) TS.

Measure the absorbance (1.6) of a 1.0 cm layer of solutions (1) and (2) at about 291 nm, using hydrochloric acid (~3.65 g/L) TS as the blank. For each of the six tablets tested, calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium using the absorptivity value of 74.2 (Å⁻¹ cm⁻¹ = 742). The amount of albendazole released is not less than 80% (Q) of the amount declared on the label.

*For 400 mg tablets*: carry out the test as described under 5.5 **Dissolution test for solid oral dosage forms** using 900 mL of hydrochloric acid (~10 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes, withdraw a sample of about 10 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature and dilute 2.0 mL of the obtained solution to 50.0 mL with hydrochloric acid (~10 g/L) TS. Use this solution as solution (1). For solution (2), dissolve 44.0 mg of albendazole RS in 10.0 mL of sulfuric acid/methanol (1%) TS and immediately dilute to 100.0 mL with of hydrochloric acid (~10 g/L) TS. Dilute 2.0 mL of this solution to 50.0 mL with hydrochloric acid (~10 g/L) TS.

Measure the absorbance (1.6) of a 1.0 cm layer of solutions (1) and (2) at about 291 nm, using hydrochloric acid (~10 g/L) TS as the blank. For each of the six tablets tested, calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium using the absorptivity value of 74.2 (Å⁻¹ cm⁻¹ = 742). The amount of albendazole released is not less than 80% (Q) of the amount declared on the label.
Carry out the test as described under **5.5 Dissolution test for solid oral dosage forms** using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank.

For each of the six tablets tested calculate the total amount of albendazole (C₁₂H₁₅N₃O₂S) in the medium using the absorptivity value of 74.2 (\( A_{1\text{cm}}^{1\%} = 742 \)). The amount in solution for each tablet is not less than 80% (Q) of the amount declared on the label.

**Related substances**

- Either method A or method B may be applied.

**A.** Carry out the test as described under **1.14.4 High-performance liquid chromatography** using the conditions given below under “Assay”, Method A.

Prepare the following solutions.

- Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R. For solution (1), transfer a quantity of the powdered tablets containing about 25 mg of Albendazole to a 50 mL volumetric flask. Add 5 mL of the solvent mixture and 20 mL of methanol R and shake to dissolve for about 15 minutes. Dilute to volume with methanol R. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with methanol R. For solution (3), dissolve about 20 mg of albendazole RS and about 20 mg of oxibendazole R in 5 mL of solvent mixture and dilute to 100.0 mL with methanol R. Inject separately 20 µL each of solutions (1), (2) and (3). Record the chromatogram for about 25 minutes.

In the chromatogram obtained with solution (3), the peak due to oxibendazole is eluted at a retention time of about 9.9 min and the peak due to albendazole at a retention time of about 13.6 minutes. The test is not valid unless the resolution factor between the peak due to oxibendazole and the peak due to albendazole is at least 3.0.

In the chromatogram obtained with solution (3), the area of any peak, other than the principal peak, is not greater than the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.0%); and

- the area of not more than one such peak is greater than 0.75 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.75%).
B. Carry out the test as described under **11.14.1 Thin-layer chromatography** using silica gel R5 as the coating substance and a mixture of dichloromethane R, glacial acetic acid R and ether R (30:7:3 v/v) as the mobile phase. Apply separately to the plate 10 µL each of the following solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of glacial acetic acid R. For solution (A), shake a quantity of the powdered tablets containing about 250 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B), use 0.1 mg of albendazole RS per mL. For solution (C), use 0.075 mg of albendazole RS per mL. For solution (D), use 0.1 mg albendazole RS and 0.1 mg oxibendazole R per mL. After removing the plate from the chromatographic chamber, allow the plate to dry in a current of warm air. Examine the chromatogram in ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (D) shows two clearly separated spots.

In the chromatogram obtained with solution (A), any spot, other than the principal spot, is not more intense than the principal spot obtained with solution (B) (1.0%) and not more than one spot is more intense than the principal spot obtained with solution (C) (0.75%).

**Assay**

- Either method A or method B may be applied.

A. Carry out the test as described under **11.14.4 High-performance liquid chromatography** using a stainless steel column (25 cm × 4.6 mm) packed with octadecylsilyl base-deactivated silica gel for chromatography R (5 µm). As the mobile phase, use a solution prepared as follows: dissolve 1.67 g of monobasic ammonium phosphate R in 1000 mL of water R, mix and filter. Mix 300 mL of this solution with 700 mL of methanol R. Prepare the following solutions.

Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 100 mg of Albendazole, accurately weighed, to a 50 mL volumetric flask. Add 5 mL of the solvent mixture and 20 mL of methanol R and shake for about 15 minutes. Dilute to volume with methanol R, mix and filter, discarding the first 15 mL of the filtrate. Dilute 5.0 mL of this solution to 50.0 mL with methanol R. For solution (2), transfer 25.0 mg of Albendazole RS to a 25 mL volumetric flask, add 5 mL of the solvent mixture and 15 mL of methanol R and shake to dissolve. Dilute to volume with methanol R. For solution (3), dilute 2.0 mL of solution (2) to 10.0 mL with methanol R. For solution (4), dissolve about 20 mg of oxibendazole R in 5 mL of solvent mixture in a 100 mL volumetric flask, add 20 mL of solution (2), mix and dilute to volume with methanol R. Operate with a flow rate of 0.7 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 254 nm.
Inject separately 20 µL each of solutions (1), (3) and (4). The test is not valid unless, in the chromatogram obtained with solution (4), the resolution factor between the peaks due to albendazole and due to oxibendazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (3) and calculate the content of Albendazole (C₁₂H₁₅N₃O₂S) in the tablets using the declared content of C₁₂H₁₅N₃O₂S in albendazole RS.

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 20 mg of Albendazole, accurately weighed, to a 50 mL volumetric flask, add 30 mL of hydrochloric acid/methanol (0.01 mol/L) VS, shake for 15 minutes and dilute to volume with the same solvent. Mix and filter, discarding the first 10 mL of the filtrate. Transfer 1.0 mL of the subsequent filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank. Calculate the content of Albendazole (C₁₂H₁₅N₃O₂S), using the absorptivity value of 74.2 ($A_{1cm}^{1%} = 742$).
Good reliance practices in regulatory decision-making for medical products: high-level principles and considerations

Please send your comments to Mrs Marie Valentin, Technical Officer, Regulatory Convergence and Networks, Regulation and Safety (valentinm@who.int), with a copy to Mrs Carolyn Doucelin (doucelinc@who.int) before 18 September 2020. Please use our attached Comments Table for this purpose.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the “Current projects” link.

If you wish to receive all our draft guidelines, please send your email address to jonesi@who.int and your name will be added to our electronic mailing list.
Good reliance practices in regulatory decision-making for medical products:
high-level principles and considerations

Acronyms

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<th>Acronym</th>
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<tr>
<td>ACSS</td>
<td>Australia-Canada-Singapore-Switzerland Consortium</td>
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<td>AMRH</td>
<td>African Medicines Regulatory Harmonisation</td>
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<td>APEC</td>
<td>Asia-Pacific Economic Cooperation</td>
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<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
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<td>ASEAN</td>
<td>Association of Southeast Asian Nations</td>
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<td>ASEANPPWG</td>
<td>ASEAN Pharmaceutical Products Working Group</td>
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<td>African Vaccine Regulatory Forum</td>
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<td>CARICOM</td>
<td>Caribbean Community and Common Market</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>Common Technical Document</td>
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<td>ICDRA</td>
<td>International Conference of Drug Regulatory Authorities</td>
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ICMRA  International Coalition of Medicines Regulatory Authorities
ICSAR  Individual Case Safety Report
IMDRF  International Medical Device Regulators Forum
IPRP  International Pharmaceutical Regulators Programme
ISO  International Organization for Standardization
IVD  In vitro diagnostic
MAGHP  Marketing Authorization for Global Health Products
MERCOSUR  Southern Common Market
MDSAP  Medical Device Single Audit Program
MRA  Mutual Recognition Agreement
NCL  National Control Laboratory
NRA  National Regulatory Authority; for the purpose of this document, this term also includes regional regulatory authorities such as the European Medicines Agency (EMA)
OECD  The Organisation for Economic Co-operation and Development
OMCL  Official Medicines Control Laboratories
PA  Pacific Alliance
PAHO  Pan American Health Organization
PANDRH  Pan American Network for Drug Regulatory Harmonization
PIC/S  Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMDA  Pharmaceuticals and Medical Devices Agency, Japan
REC  Regional Economic Communities in Africa
SEARN  South-East Asia Regulatory Network
SADC  Southern African Development Community
SRA  Stringent Regulatory Authority
TGA  Therapeutic Goods Administration, Australia
UHC  Universal Health Coverage
UMC  Uppsala Monitoring Centre
U.S. FDA  US Food and Drug Administration
WAHO  West African Health Organization
WHO  World Health Organization
WHO PQ  WHO Prequalification
WLA  WHO Listed Authorities
WHO-NNB  WHO-National Control Laboratory Network for Biologicals
ZAZIBONA  Zambia, Zimbabwe, Botswana and Namibia; initial participants of the SADC collaborative procedure for the joint assessment of medicines
1. Background

The World Health Organization (WHO) supports the implementation of reliance on other regulators’ work as a general principle in order to make the best use of available resources and expertise. This principle enables leveraging the output of others whenever possible while placing a greater focus at the national level on value added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to, in-country vigilance and market surveillance and control activities and oversight of local manufacturing and distribution. Reliance approaches facilitate timely access to safe, effective and quality-assured medical products (see 5. Scope) and can help in regulatory preparedness and response, particularly during public health emergencies.

Good Reliance Practices (GReIP) are anchored in the overarching Good Regulatory Practices (GRP) (1) which provide a means for establishing sound, affordable and effective regulatory oversight of medical products as an important part of health system strengthening. If implemented effectively, GRP can lead to consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes. National regulatory authorities (NRAs) are encouraged to adopt these best practices in order to ensure that they are using the most efficient regulatory processes possible.

An ongoing initiative at WHO aims at establishing and implementing a framework for evaluating regulatory authorities and designating them as WHO-Listed Authorities (WLAs) (2). Based on benchmarking using the WHO Global Benchmarking Tool (GBT) (3), along with a performance evaluation process, WHO will assess the regulatory authority’s performance and maturity level in order to qualify a regulatory authority as a WLA and thereby provide a globally recognized, evidence-based and transparent system that can be used by NRAs as a reference for the selection of reference regulatory authority(ies) to practice reliance. A list of reference regulatory authorities is available on the WHO Website for NRAs to refer to (4).

The WHO held a consultative meeting in September 2019 in order to solicit input on the nature, structure and overall content of a document outlining GReIP. The meeting concluded that the Pan American Health Organization (PAHO)/Pan American Network for Drug Regulatory Harmonization (PANDRH)’s concept note and recommendations on regulatory reliance principles (5) should be used as a starting point for the development of a WHO GReIP document. The high-level document would be complemented in a second step by a repository of case studies, practice guides and examples of practical applications of GReIP.
2. Introduction

The United Nations Sustainable Development Goals and the drive for Universal Health Coverage (UHC) require that patients have access to quality-assured and safe medical products, hence, strong regulatory systems for medical products remain a critical element of well-functioning health systems and an important contributor to improving access and ultimately achieving UHC.

Establishing and sustaining mature regulatory systems is an enterprise that requires adequate resources including skilled and capable human resources and significant public investments. Moreover, the globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains have led regulators to recognize the importance of international cooperation in order to ensure the safety, quality and efficacy of locally used products. In view of the extent and complexity of regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative and more effective forms of collaboration in order to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where most needed.

Reliance represents a smarter and more efficient way of regulating medical products in a modern regulatory world. Towards this end, countries are encouraged to formulate and implement strategies to strengthen their regulatory systems consistently with GRP, including pursuing regulatory cooperation and convergence, as well as reliance. Reliance brings benefit to patients and consumers, the industry, national governments, as well as the donor community, and international development partners by facilitating and accelerating access to quality-assured, effective and safe medical products.

There is a long history of enhancing the efficiency of regulatory systems through reliance. The WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (6), introduced by WHO in 1969, is a form of reliance providing assurance to countries participating in the Scheme about the quality of pharmaceutical products. The European Union (EU) introduced the mutual recognition procedure for marketing authorizations between Member States in 1995, and outcomes of Good Manufacturing Practice (GMP) inspections have been shared for years in the context of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) (7) and mutual recognition agreements.

The use of reliance was more recently investigated by WHO through a survey conducted on behalf of the International Pharmaceutical Regulators Programme (IPRP) (8). The results showed that regulatory reliance is a broadly accepted and widely practised approach in the area of medical products, especially among the participating well-resourced regulatory authorities. At the same time, responses also reflected an evolving situation marked by varying degrees of experience and promise in the use of reliance-based approaches. While the
use of reliance in some regions may be characterized as an emerging trend, the commonly
stated goals are to bring efficiency, to help strengthen regulatory systems and to optimize the
use of resources. The results and suggestions from this survey were taken into account for the
preparation of this document.

Given the increased prevalence and importance of reliance in the regulatory oversight of
medical products, countries have requested WHO to develop practical guidance on the topic
while ensuring that approaches meet the intended objectives. This document, and the
companion documents that will follow, are intended to assist countries in implementing a
sound, evidence-based, practical and effective approach to reliance.

3. Purpose

The objective of this document is to promote a more efficient approach to regulatory
oversight, thereby promoting access to quality-assured, effective and safe medical products.

The document aims at presenting the overarching principles of regulatory reliance in the field
of oversight of medical products and the use of reliance as a tool for enhancing efficiency of
regulatory oversight.

This document is intended to provide high-level guidance, definitions, key concepts and
considerations in order to guide reliance mechanisms and activities, illustrative examples of
reliance approaches and conclusions. It will be complemented by a “reliance toolbox”
consisting of practice guides, case studies and a more comprehensive repository of examples.

4. Scope

This document covers reliance activities in the field of regulatory oversight of medical
products (i.e. medicines, vaccines, blood and blood products and medical devices including in
vitro diagnostics and other health products), addressing all regulatory functions as defined in
the GBT spanning the full life cycle of a medical product - namely registration and marketing
authorization, vigilance, market surveillance and control, licensing establishments, regulatory
inspection, laboratory testing, clinical trials oversight, and NRA lot release (3).

In addition, this document is intended for all NRAs, irrespective of their level of maturity or
resources, as well as policy makers, governments, the industry and other developers of
medical products, and other relevant stakeholders.

The concept of reliance can cover all types of medical products and regulatory activities.
Special consideration could be given to using reliance approaches for medical products
addressing priority diseases with unmet medical needs, medical products to be used in public
health emergencies or during shortages as well as for orphan medical products.
5. Definitions and key concepts

5.1 Definitions

Definitions are essential to ensure a common understanding of concepts and clarity in interpreting guidance related to reliance. In addition to the definitions provided below, reference is made to the WHO good regulatory practices document (1), which includes definitions for harmonization, convergence and other relevant terms.

**abridged regulatory pathways.** Abridged regulatory pathways are regulatory procedures facilitated by the use of reliance, whereby the regulatory decision is solely or widely based on the application of reliance. Normally this would also involve some degree of work by the relying NRA (see 6.2.4 Risk-based approach). The expectation is that the use of reliance in these pathways would save resources and shorten the timelines compared to the standard pathways, while ensuring that the standards for regulatory oversight are maintained.

**assessment.** For the purpose of this document, the term “assessment” covers the outcome of any evaluation conducted for a regulatory function (e.g. evaluation for a clinical trial application, evaluation of an initial authorization for a medical product or any subsequent post-authorization changes, evaluation of safety data, evaluation as part of an inspection, etc.).

**equivalence of regulatory systems.** Equivalence of regulatory systems implies a high degree of similarity between two regulatory systems as mutually established and documented through objective evidence. Equivalence can be established using criteria and approaches such as similarity of the regulatory framework and practices, adherence to the same international guidelines and standards, experience gained through the use of assessments for regulatory decision-making, joint activities and exchange of staff, among others. The expectation is that equivalent regulatory systems should lead to similar standards and levels of regulatory oversight or “levels of control”.

**international standards and guidelines.** For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant internationally recognized standards (e.g. International Organization for Standardization (ISO) or pharmacopoeial standards) and guidelines (e.g. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) or PIC/S guidelines).

**mutual recognition agreement.** According to a definition issued by the Organisation for Economic Co-operation and Development (OECD), mutual recognition agreements are “a principle of international law whereby states party to mutual recognition agreements recognize and uphold legal decisions taken by competent authorities in another member state. Mutual recognition is a process which allows conformity assessments (of qualifications, product…) carried out in one country to be recognized in another country” (9).
recognition. The acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority is sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

reference regulatory authority. For the purpose of this document, the reference regulatory authority is a national or regional authority or a trusted institution such as WHO prequalification (WHO PQ) being relied upon by another regulatory authority.

regional regulatory system. A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework including or excluding a common legal framework. The common framework must at least ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework.

reliance. The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

sameness of product. For the purpose of this document, the sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying authority and the product approved by the reference regulatory authority). All relevant aspects applicable to drugs, medical devices and in vitro diagnostics have to be considered in order to confirm that the product is the same or sufficiently similar (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same active pharmaceutical ingredient suppliers, etc.). Additionally, supporting safety, efficacy and quality studies, indications and conditions of use, and so on, should be the same. The impact of potential justified differences should be assessed by the manufacturer (for the purpose of this document, manufacturer also means marketing authorization holder) and the relying NRA in determining the merit of using foreign regulatory assessments or decisions.
**stringent regulatory authority.** A regulatory authority which is: (a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or (b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) (10).

**work-sharing.** Work-sharing is a process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. The opportunities for work-sharing include, but are not limited to: jointly assessing applications for authorization of clinical trials, marketing authorizations or good practices inspections, joint work in the post-marketing surveillance of medical product quality and safety, joint development of technical guidelines or regulatory standards, and collaboration on information platforms and technology. Work-sharing also entails the exchange of information consistent with the provisions of existing agreements and compliant with each agency’s or institution’s legislative framework for sharing such information with other NRAs.

A **joint activity** is a form of work-sharing whereby a regulatory task is conducted by two or more NRAs in collaboration in order to share their assessments, benefit from each other’s expertise and discuss any shortcomings of the data being evaluated. For example, a joint assessment is a procedure in which the same application is simultaneously submitted to two or more NRAs in order for the (assigned) NRAs to conduct their evaluations in parallel and share their respective scientific assessments with each other (e.g. the different modules for quality, nonclinical and clinical data can be assigned to different NRAs for review). The NRAs participating in the joint assessment can combine their list of questions or deficiencies to send to the manufacturer and base their respective independent regulatory decision on the outcome of these assessments. Similarly, a joint inspection is an inspection involving two or more NRAs sharing the activities and assessment performed during an inspection.

**5.2 Key concepts**

The diagram below illustrates some of the key concepts explained in the document, notably how NRAs can gain efficiencies in their regulatory operations and how they avoid duplication by using reliance approaches.
5.2.1 Reliance versus recognition

Reliance may take many forms and reflect varying degrees of application in recognizing or taking account of the assessments, decisions or any other authoritative information available from other authorities and institutions. Recognition may be seen as a special and more formalized approach to reliance whereby one regulatory authority recognizes the decisions of another regulatory authority, system or institution, obviating the need for additional regulatory assessment in reaching its own decision. Recognition usually requires formal and binding legal provisions.
5.2.2 Unilateral vs. mutual reliance/recognition

Reliance and recognition can be unilateral, for example, when a country chooses to rely on or formally recognize the assessment from another country unilaterally and without reciprocity. In other cases, mutual reliance or recognition may be based on binding mutual agreements or treaties negotiated at the level of governments. These agreements may take considerable time and resources to set up as the regulatory systems involved need to be mutually assessed and shown to be equivalent before implementation. The demonstration of equivalence of regulatory systems is normally a prerequisite to mutual reliance or recognition.

5.2.3 Life cycle approach

The concept of reliance for regulatory oversight of medical products should be applied across the full life cycle of medical products and all regulatory functions (see 5. Scope). While reliance approaches are widely used for the initial authorization of medical products, it is equally important to consider the use of reliance for vigilance and other post-authorization activities given the substantial regulatory resources required for evaluating safety and post-approval changes over the product life cycle. Reviewing post-approval changes to a product approved by a different authority may present some challenges. Therefore, if an NRA has relied upon another NRA’s assessment for its initial approval, there is a strong benefit for similar reliance measures for post-approval changes and vigilance activities. This also avoids the situation of different changes being accepted in the originating and receiving countries over time.

5.2.4 Risk-based approach

Each NRA should define its own strategy regarding the appropriate risk-based approach to reliance that considers factors, such as the type and source of products evaluated, the level of resources and expertise available in the NRA, the public health needs and priorities of the country, and opportunities for reliance. Using marketing authorization as an example, one could envisage four different approaches and levels of reliance involving an increasing degree of additional assessment by the relying NRA:

i. Verification of sameness of the product to ensure that the medical product is the same as the one that has been assessed by the reference regulatory authority (see 8.1e Sameness of the product in different jurisdictions).
ii. Confirmation of applicability of the assessment outcomes of another authority for regulatory decision-making in the national context, for example, in terms of legal and regulatory settings, benefit-risk assessment, co-morbidities, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability. In case of differences, such as in target population, epidemiology and other features of the disease, concomitantly used medicines and other factors that can substantially affect the benefit–risk profile of a medicine as well as quality parameters, especially in relation to the stability under different climatic conditions, appropriate justification should be provided by the Applicant.

iii. Abridged assessment of the quality, safety and efficacy/performance data taking into account information in the assessment reports of the reference regulatory authority.

iv. Joint assessment or work-sharing between two or more regulatory authorities. This could take various forms, including a primary review by one authority followed by a joint assessment session to finalize the assessment report and comments, or a distribution of the different modules (quality, non-clinical and safety/efficacy) between authorities.

Regardless of the approach, the expectation is that reduced timelines compared to standard timelines are applied when using reliance.

Similar models can also be developed or used for other regulatory functions (e.g. inspection).

### 5.2.5 Regional reliance mechanisms

In some regions, an assessment for medical products can be conducted centrally based on a regional regulatory system for a group of countries. In some regional reliance mechanisms, the regional decision is binding on the member states (e.g., EU processes). In others, the regional decisions are recommendations that member states take into consideration when making their national regulatory decisions (e.g. Southern African Development Community (SADC) collaborative procedure (ZAZIBONA, which stands for Zambia, Zimbabwe, Botswana and Namibia), the Gulf Health Council (GHC) and the Caribbean Regulatory System (CRS)).
6. Principles underpinning good reliance practices

In developing a strategy on the use of reliance in regulatory functions and activities, an NRA should consider possible approaches in the context of the needs and characteristics of the national health and regulatory system. The decision to practice reliance should take into consideration the existing capacities, regulatory systems’ needs, the availability of an authority that the NRA can rely upon with confidence, and how reliance can complement their own capacities to drive efficiencies and the optimal use of resources. Reliance is not a lesser form of regulatory oversight but rather a strategy seeking to make the best use of the available resources in any given setting. This would allow the allocation of resources to other areas of regulatory functions, such as in-country vigilance and post-authorization activities and increase the effectiveness of the local regulatory oversight. In addition, reliance can lead to more evidence-based and better-quality decisions.

The following principles are meant to complement and expand upon the basic principles of GRP and are based on the principles presented in the PAHO/PANDRH concept note and recommendations on regulatory reliance principles (5).

6.1 Universality

Reliance applies to all NRAs irrespective of their levels of maturity or resources. Lack of resources or capacity are not the exclusive drivers for reliance. Different NRAs use reliance for different reasons, either to increase or build capacity when they have the requisite expertise in house, but just not enough of it to perform their regulatory work as efficiently as they would like. Other NRAs use reliance to increase expertise to which they otherwise would not have local access to. Indeed, reliance is relevant for all resource settings, representing an increasingly important mechanism for improving regulatory efficiency.

6.2 Sovereignty of decision-making

The decision to practice reliance, and how best to implement reliance, rests with the health regulatory authority of the country. Reliance does not imply dependence. In applying reliance in their daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.

6.3 Transparency

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent regarding the standards, processes and approaches adopted in implementing reliance measures. In addition, the basis and rationale for relying on a specific entity should be disclosed and fully understood by all parties. NRAs should engage with all stakeholders including industry to ensure the appropriateness and awareness of the reliance processes.
Furthermore, NRAs should conduct transparent regulatory operations and decision-making, not only as a fundamental principle of GRP, but also towards building trust and maximizing opportunities for cooperation and reliance as part of a shared regulatory community responsibility. In other words, regulatory authorities are an increasingly important audience and beneficiaries of measures that promote transparency in regulatory oversight through the publishing and sharing of regulatory information. NRAs seeking to act as reference agencies are encouraged to issue public assessment reports in a common language documenting their regulatory decisions. Relying NRAs should use these reports where available as the primary source to inform assessment. If no public assessment reports are available or when additional information of a confidential nature is required, the manufacturer should provide such assessment report. If the relying NRA insists to obtain the non-public assessment reports from the reference agency, those reports may be provided by the reference agency with the consent of the manufacturer, if needed.

6.4 Respect of national and regional legal basis

Reliance practices should be coherent with national and regional legal frameworks and medical products' policy and supported by clear mandates and regulations that enable the efficient implementation of reliance as part of government policy on good regulation. The driving force behind the adoption of these legal frameworks should be the efficiencies and capacity to be gained by reliance, not the minimization of resources for regulatory functions. Where regulations including explicit provisions regarding the application of reliance do not exist, reliance may still be adopted through the interpretation of existing regulations provided that the legal framework does not explicitly preclude the application of reliance approaches by the NRA. Implementing reliance can be done through policy changes as long as it is broadly consistent with the legislation. If prohibitions to apply reliance exist, they should be considered for revision within a reasonable timeframe.

6.5 Consistency

Reliance on a specific assessment or decision from another authority should be established for specific and well-defined categories of products and processes. The scope of regulatory activities where reliance may be practised should be clearly defined and the process for practising reliance should be transparent and predictable. Thus, the expectation is that reliance shall be applied consistently for products/processes in the same predetermined categories.
6.6 Competency

The implementation of reliance approaches requires that NRAs have built the necessary competencies for critical decision-making. Setting up the reliance approach will normally require the involvement of senior regulatory staff, managers and experts who are competent to make the best use of foreign information in the local context. NRAs should also maintain the appropriate scientific expertise of their staff needed for activities where they do not apply reliance, for example, such as in local adverse event monitoring, market surveillance and control, national labelling and product information activities and for approval of locally manufactured products.

Equally, authorities being relied upon should possess and maintain competencies and operate within a robust and transparent regulatory system, underpinned by international standards and guidelines as well as good regulatory practices and a well-functioning quality management system (11). Competencies may be benchmarked using transparent processes to develop trust and build confidence in the reference authorities.

7. Considerations

A number of considerations can guide reliance approaches and facilitate their successful implementation. These considerations include general aspects as well as barriers that NRAs need to overcome and enablers that will help in implementing reliance approaches. The non-exhaustive list of considerations presented below will be further elaborated in the case studies, practice guides and the reliance repository.

Reliance is encouraged in any settings, for example, when supported by common legal or regulatory framework in a regional regulatory system, by bilateral agreements, by mutual recognition agreements or on a purely voluntary, networking or ad-hoc basis.

As a principle, reliance should be based on the original assessment and not on a decision that was itself based on reliance from another assessment (i.e. no reliance on a fully relied upon outcome).
7.1 General considerations
7.1.1 Reliance anchored in a national regulatory authority strategy

In addition to having a legal basis supporting, or at least not precluding reliance approaches (see 7. Principles underpinning good reliance practices), the application of reliance should be anchored in the NRA’s strategy, endorsed by senior management and in the respective high-level National Policy in order to provide a mandate, direction and expectations to NRA staff, guiding them in their day-to-day work. The strategy should be further detailed in procedures and integrated in processes to ensure that maximum benefits accrue. It should also include considerations on a sustainable funding model for the NRA when implementing reliance. The strategy should be published in order to make it accessible and understandable to external stakeholders. Additionally, the implementation of reliance should be supported by training and periodic reviews to ensure that standards are being maintained, to assess whether or not objectives are being met, and to make refinements where warranted.

Implementing reliance should not negatively impact the financial sustainability of the NRA.

NRAs that are practising reliance should establish and publish a list of reference regulatory authorities together with the criteria used for identifying them. The NRA should decide and establish the criteria they want to apply for the selection of the reference regulatory authorities (e.g. application of international standards, longstanding recognition in the international community, proximity and commonality of medical products, etc.). In order to qualify reference regulatory authorities or a specific oversight of a regulatory function, an NRA may refer to an assessment performed by an independent organization (e.g. WHO Benchmarking and WLA, ISO accreditation, the Medical Device Single Audit Program (MDSAP), PIC/S, etc.).

WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance in their country and region and to share their experiences with other regulatory authorities. Where possible, specific measurement of the impact of reliance is strongly encouraged and the respective NRA should prospectively establish the metrics they will employ to measure the impact of using reliance in their regulatory decision-making and the timing when such an impact assessment will be undertaken. These metrics may include, for example, cost savings, efficiencies in the number of products reaching markets or time to market, a redirection of scarce resources to areas of higher regulatory risks, and so on.
7.1.2 Cultural change

The implementation of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on other NRA outputs. It is essential that the benefits of the strategy be understood and supported at the operational level and that staff expected to implement reliance approaches have input into their development.

This will require engagement, willingness, effective preparation, messaging and support from management and peers that articulates the importance of reliance in better addressing workload pressures without minimizing the rigor of regulatory work or causing the loss of scientific and regulatory competence and capacity. In fact, the use of assessments and information from other trusted regulatory authorities can help build capacity and competence (e.g. through exposure to the reviews and decisions of the reference authority, networking, twinning, staff visits/staff exchanges, etc.). Furthermore, the effective use of such information within the local context requires skills, ability and experience. Thus, the skill set and competency framework needed to practise reliance will need to be developed in the NRA’s workforce.

Senior management, reviewers, inspectors and other staff should build confidence and trust in work that has been done by other NRAs or trusted authorities. Building trust in other NRAs’ work requires time and a change in the culture within the relying NRA. Some regulatory authorities and systems already practise reliance and that experience should be leveraged to promote acceptance and avoid pitfalls.

Trust should also be built with the public and healthcare professionals in order to inform and assure them that the use of reliance offers a more efficient regulatory oversight.

7.1.3 Flexibility in approach: “one size doesn’t fit all”

Following the principles listed above, reliance strategies should be tailored to the needs of the national health and regulatory systems. NRAs may choose to rely on others as part of their routine regulatory oversight and/or during special circumstances such as public health emergencies. Reliance is a tool offering flexibility to NRAs. Whatever the approach, the NRA needs to consider its own capacities and to establish clear goals and efficient processes and ensure the standards and criteria are transparent and well established when adopting reliance.
7.1.4 Implementing reliance needs investment of resources and time

As stated above, reliance should increase the efficiency of a regulatory system in a country and/or region. Nevertheless, the implementation of reliance approaches will first require time and investment of resources. This may include but may not be limited to: legislative changes and the development of guidance documents, the development of approaches and elaboration of procedures and processes, confidence-building through parallel or joint reviews and supported by staff exchanges, the training of staff, dialogue with industry and other stakeholders, as well as the establishment of, or access to, information-sharing platforms. To the best extent possible, the use of publicly available information should also be pursued.

7.1.5 “Sameness” of the product in different jurisdictions

One of the most critical aspects when applying reliance is the verification of the “sameness” of the medical product (see 6.1 Definitions) in different jurisdictions. Reliance can only be applied if the NRAs have the assurance that the medical product assessed by the reference regulatory authority is essentially the same as the one submitted to the NRA, intending to use a foreign assessment as the basis for its own assessment and regulatory decision-making. The role of the manufacturer is essential here in order to confirm the sameness of a product and to provide the same documentation to different NRAs to the exception of the additional country specific information submitted for review such as product stability data according to the stability zone. As part of the process, the manufacturer should confirm in the application that the product is the same and that the dossier contains the same information as much as possible, taking into consideration any potential national requirements.

If the dossier is not submitted simultaneously to the agencies, the manufacturer should highlight any new information acquired about the product since the dossier was submitted to the reference agency with the corresponding assessment.

7.1.6 The role of industry

Industry plays a crucial role in the successful application of reliance mechanisms by NRAs. While industry is widely supportive of reliance as a concept and practice that can bring about efficiency gains, industry must also have clear guidance on its application and see meaningful benefits.

Industry’s support and stringent adherence to the factors that give validity to the reliance process is vital for filing applications in multiple countries or regions, ensuring the sameness of products submitted to reference regulatory authorities and relying NRAs, and sharing unredacted and complete information.
Review and discussion of pilot programs to quickly adapt and improve guidance will be key to benefit from key learnings and improve implementation. Collaboration and dialogue between all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance.

7.1.8  Reliance in case of a public health emergency

In case of a public health emergency, reliance approaches represent an even more essential tool and should be given more importance to accelerate access to medical products needed in the context of the emergency.

7.2  Barriers

7.2.1  Lack of political will

The lack of political will and support at government level can make it difficult for NRAs to implement or facilitate reliance in their daily practice, even if a legal basis is established supporting (or not precluding) reliance and NRAs’ support reliance as a strategy and approach.

7.2.2  Lack of accessible information and confidentiality of information

The lack of access to complete assessments of reference regulatory authorities can pose a major barrier to implementing effective reliance strategies. Reference regulatory authorities should strive to make assessments and other regulatory information publicly available.

Non-public regulatory reports might also be obtained directly from the manufacturer when the company is able to access these reports from the reference regulatory authority. If this is not possible, the relying NRA should approach the reference regulatory authority for the non-public regulatory reports. In these cases, having arrangements between NRAs regarding the exchange of confidential information would facilitate the implementation of the reliance process.

Sensitive, non-public information included in unredacted assessment or inspection reports can also be shared between regulatory authorities upon request. This may include confidential, commercial, trade secret or personal information. In some circumstances, the sharing of such information may require the prior consent of the manufacturer. The sharing of personal information may also require prior consent from the individual in order to comply with data protection regulations.
Given the sensitivity of such non-public information, NRAs may require that confidentiality agreements be signed which govern the exchange, management and disclosure of such information in order to ensure that the confidential nature of the information is protected by relying NRA. Such information should always be exchanged using secure channels or information-sharing platforms.

7.2.3 Other considerations

Additional barriers can include issues around language such as lack of common language or translation difficulties/cost, differences in country-specific regulatory requirements and evidentiary standards, the lack of regulatory alignment of product risk-classifications and inconsistent practices regarding product modifications in the area of medical devices including in vitro diagnostics, the lack of acceptance of foreign clinical data and real-world evidence, the level of detail in regulatory reports, different levels of competencies and, as previously noted, internal resistance and insufficient knowledge of the reference regulatory authority and how it operates. All such factors should be considered in developing the appropriate reliance strategies, as will be further elucidated in the companion documents to follow.

7.3 Enablers

7.3.1 Trust

Trust is a critical element since the reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Consequently, initiatives that foster trust among regulatory authorities are essential to promoting reliance. Trust is developed through increasing familiarity and understanding in what stands behind regulatory outputs. By sharing information, including the standards applied to regulatory decisions, working together and learning each other’s ways of working, confidence can be built throughout the entire organization, which thereafter leads to the effective use of reliance in regulatory work. Trust can be built in phases, starting with the exchange of assessment reports, and moving to work-sharing or joint assessments in a stepwise approach. Regulatory authorities may also consider using applications of lower risk (see 6.2.4 Risk-based approach) to initiate reliance processes.

7.3.2 Convergence and harmonization

Convergence and the harmonization of requirements and standards are important enablers of regulatory cooperation and reliance. The more requirements and standards are alike, the more opportunity for collaboration and reliance exists. The implementation of the ICH Common Technical Document (CTD) and the electronic CTD (eCTD) as a common format for regulatory submissions around the globe is just one example how harmonization can facilitate and enable reliance.
The differences in standards and practices, however, do not prevent one authority from relying on another, particularly when the relying authority has limited capacity and expertise. The system upon which an NRA relies should be at least equivalent to or superior to the standards it applies. As a matter of good practice, NRAs should preferably rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines.

7.3.3 Information-sharing and dialogue between regulators

Information-sharing is an essential part of reliance and NRAs are encouraged to share information and good practices with other NRAs as much as possible. The increasing dialogue between regulators is seen in the growing number of international initiatives such as the IPRP or the International Conference of Drug Regulatory Authorities (ICDRA), as well as regulatory information- and work-sharing networks such as PANDRH, the South-East Asia Regulatory Network (SEARN), regulatory networks in the Regional Economic Communities (RECs) under the African Medicines Regulatory Harmonisation (AMRH) Initiative or the Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group (PPWG), International Coalition of Medicines Regulatory Authorities (ICMRA) and so on, which are great facilitators for reliance.

Scientific and technical events, such as ICH and ICDRA conferences, are also platforms that promote the dissemination of regulatory information and support building knowledge and trust among NRAs.

As already mentioned, the sharing of confidential information should always occur through secure channels or via secure platforms. Investment in the respective IT infrastructure is therefore important to enable reliance.

7.3.4 Economic or legal integration

In situations where there is economic or legal integration in a region or for a group of countries, reliance is facilitated and strengthened by the existing mutual provisions, such as the Asia-Pacific Economic Cooperation (APEC), ASEAN, the Caribbean Community and Common Market (CARICOM), the EU, the Eurasian Economic Union, Gulf Cooperation Council (GCC), Pacific Alliance (PA), the RECs in Africa, or the Southern Common Market (MERCOSUR).
7.3.5 Engagement of stakeholders

All relevant stakeholders, including industry, healthcare professionals, policy makers and the public, should be engaged and/or informed in order to increase the understanding and acceptance of reliance approaches as they present some clear benefits for all parties involved. Communications and engagement with stakeholders should be tailored to the target audience.

8. Conclusions

Reliance is seen by a growing number of regulatory authorities as an important means of improving the efficiency of regulatory operations in the oversight of medical products. It allows NRAs to make the best use of resources, build expertise and capacity, increase the quality of regulatory decisions, reduce duplication of effort and, ultimately, promote timely access to safe, efficacious and quality-assured medical products. By adopting reliance measures whenever possible within a well-structured framework, underpinned by national or regional policies and strategies, regulators may focus their resources on key activities that cannot be undertaken by others and that contribute to public health.

Reliance represents a “smarter” form of regulatory oversight based on constructive regional and international collaboration, one that will also facilitate and promote convergence and the use of common international guidelines and standards, as well as ensure access to medical products to patients worldwide with more predictable and faster approvals.

Reliance does not represent a less stringent form of regulatory oversight nor an outsourcing of regulatory mandates or a compromise to independence. On the contrary, the decision to “regulate through reliance” is the hallmark of a modern and efficient regulatory authority.

The inclusion of reliance-related provisions by NRAs as part of their flexible regulatory pathways is encouraged and should be considered for all regulatory functions over the medical product life cycle, as appropriate.

The principles and considerations presented in this document should be taken into account when implementing regulatory reliance frameworks or strategies. Effective implementation of reliance will benefit not only NRAs but also patients, healthcare providers and industry.

While reliance may be viewed as a particularly useful strategy for low-resourced regulatory authorities, it is equally relevant for well-resourced NRAs. Reliance is an approach to be used by all NRAs and, as such, should become an integral part of regulatory operations.
9. Annex 1: Examples

Regulatory reliance can take many forms and encompasses a broad array of regulatory approaches and practices that can involve two or more regulatory authorities. In addition, it can be limited to a discrete regulatory process or function or include the full scope of regulatory functions over the entire life cycle of a medical product.

There are many examples around the world that illustrate the current use of reliance and the diverse models in which national regulatory authorities (NRAs) leverage the work done by others.

Examples are given below to illustrate the different points addressed in this document and to show the use of reliance in the different regulatory functions. The list below is not exhaustive but just an illustration of the current practices of reliance taking place globally. It may be replaced in future by a comprehensive repository of reliance approaches to be established as a part of the Good Reliance Practices (GRelP) toolbox.

a) Clinical trials

Work-sharing for clinical trial assessment is happening in some regions, such as the Voluntary Harmonisation Procedure in the European Union (12) and via the African Vaccine Regulatory Forum (AVAREF) (13). By assessing clinical trial applications together, NRAs and, in some cases, ethics committees from different countries, can benefit from the assessments performed by the different participating countries with a view to facilitating and ensuring the robustness of the approval process across countries. The AVAREF platform has been instrumental in building the expertise and capacity of regulators and ethics committees, promoting the use of international standards and expediting clinical trial assessments and decisions for medical products of high public health interest in both emergency and normal circumstances. Towards this end, a guideline and platform for joint assessment of clinical trials applications, as well as Good Clinical Practices (GCP) site inspections, have been developed and implemented in order to facilitate product development, regulatory decision-making and access to promising new medical products (14).
b) Marketing authorization

Abridged regulatory pathways using reliance for initial marketing authorization

Several procedures are available through stringent regulatory authorities (SRAs) (e.g. EMA, Health Canada (HC), the Pharmaceuticals and Medical Devices Agency (PMDA), Swissmedic, U.S. FDA) or the World Health Organization Prequalification (WHO PQ) Programme in order to enable the use of an abridged regulatory pathway by the relying NRAs.

Among those procedures, the EU Article 58, also referred to as European Union Medicines for all (EU-M4 all) (15), the Swissmedic Marketing Authorisation for Global Health Products (MAGHP) (16) procedures and the WHO Collaborative Registration Procedure (CRP) (1) are three examples of abridged regulatory pathways using reliance to facilitate the registration of medicinal products in target countries.

In addition to facilitating in-country registration, the EU Article 58 and the Swissmedic MAGHP procedures provide experts from target NRAs the opportunity to both observe and participate actively in the assessment and scientific advice procedures, with the aim of building their own capacities and to establish confidence in the processes.

The CRP facilitates the assessment and accelerates the national registration of WHO prequalified medical products and medicines approved by an SRA. The CRP operates by providing unredacted assessment, inspection and performance evaluation (in the case of in vitro diagnostics) reports upon request (and with the consent of the manufacturer) to participating NRAs, primarily in low- and middle-income countries. The procedures are detailed in WHO guidelines, which also include guidance on how receiving NRAs can make the most efficient use of the reports in reaching their own decisions. Participating NRAs are expected to reach a decision on authorization within 90 calendar days (regulatory time). The CRP tool has shown to be successful in both accelerating decisions in countries and building the capacity of regulatory authorities.

The WHO Certificate of a pharmaceutical product (CPP) is also being used as a reliance tool, in lieu of full or partial assessment for marketing authorization (18). If a CPP is provided, it is being used in lieu of a full or partial review and assessment is accelerated. Such procedures currently exist in Benin, Bolivia, Bolivia, Cameroon, Congo, Cuba, Curacao, Guinea, Haiti, Hong Kong and Honduras.
Quality information

Many NRAs, as well as the WHO Prequalification Programme (WHO PQ), recognize Certificates of Suitability to the monographs of the European Pharmacopoeia (CEP) (19) for active pharmaceutical ingredients (API) as a validation of the quality of a certain API. Some countries also recognize the Confirmation of API Prequalification (CPQ) issued by the WHO PQ for APIs (20). These two examples not only provide assured mechanisms of reliance, but also reduce the documentation requirements for countries that recognize these certificates. Where a CEP or CPQ is issued, the receiving NRA does not have to duplicate the API assessment but can focus on specific sections not covered under CEP or CPQ.

Work-sharing

The Australia-Canada-Singapore-Switzerland Consortium (ACSS Consortium) (21) is a coalition which was formed in 2007 by “like-minded” medium-sized regulatory authorities in order to promote work-sharing based on greater regulatory collaboration and the alignment of regulatory requirements. The ACSS Consortium explores opportunities for information- and work-sharing initiatives in areas including biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. The Consortium capitalizes on each country’s area of strength, addresses gaps in science, knowledge and expertise and leverages resources to help expedite risk assessment processes, while maintaining or raising quality and safety standards. The Consortium builds on existing international networks, initiatives and mechanisms in order to advance work- and information-sharing along health product life cycles.

Joint assessments

Joint assessments can provide significant benefits to NRAs by sharing the workload, building capacity by bringing broader experience and expertise together, and helping to build trust in one another’s assessments and decision-making processes. Similarly, industry can benefit from a common review process and set of questions in terms of both resource and time-savings as compared to interacting separately with multiple countries. In recognition of these benefits, a growing number of joint assessment initiatives have been established within the framework of regional regulatory networks, sometimes driven by the higher-level priorities of economic blocks seeking to create common markets.
Examples of joint assessments initiatives include those in the Regional Economic Communities in Africa (East African Community (EAC) (22), ZAZIBONA (23) in the SADC, the Economic Community of West African States (ECOWAS)/West African Health Organization (WAHO) (24), the Association of Southeast Asian Nations (ASEAN) Joint Assessment Coordinating Group (25), and so on.
Mutual recognition

The EU system is an example of highly integrated regulatory cooperation and its multiple regulatory pathways depend heavily on work-sharing, recognition and other forms of reliance. The various routes to the approval of medicines in the EU system are based on a single assessment system so that any assessment report from any of the agencies in the EU network can be used as a basis for reliance by other regulators. In this specific case, a strong and common legal framework and harmonized regulatory standards shared among all EU countries enabled and facilitated reliance and recognition (26).

c) Post-approval changes

Following the same principles as for initial marketing authorization, reliance can also be applied broadly for assessing post-approval changes already approved by NRAs considered as reference authorities. In the case of CRP, for example, the participating NRAs for prequalified products are informed by WHO of any variations approved by WHO PQ Team (17).

The Health Sciences Authority (HSA) in Singapore is applying a verification route with shortened timelines for approving post-approval quality and product label changes, which aims to enable greater leveraging of reference agencies’ assessments, minimize duplication of effort and enhance process efficiency as part of HSA’s on-going effort, in particular for effective life cycle management for registered therapeutic medicinal products. To qualify, the proposed changes must be identical to those approved by one of HSA’s five reference agencies, accompanied by the proof of approval of that reference agency as well as the approved product label of that reference agency where applicable (27).

d) Testing and lot release

Network of Official Medicines Control Laboratories

The Network of Official Medicines Control Laboratories (OMCLs) support regulatory authorities in controlling the quality of medicinal products available on the market. Collaboration within the Council of Europe’s General European OMCL Network (GEON) (28) makes the best use of resources via resource pooling and avoids duplication of work or testing. Some of the main goals of the Network are to set mutual recognition, within the members of the networks, of tests carried out by OMCLs at the national level, coordinate activities among the OMCLs, and facilitate knowledge and work-sharing.
Lot release and quality monitoring of vaccines and other biologic products

Launched in 2017, the WHO-National Control Laboratory Network for Biologicals (WHO-NNB) (29) brings together National Control Laboratories (NCLs) and NRAs of vaccine-producing and vaccine-recipient countries, WHO contract laboratories, manufacturer associations, WHO Regional Offices and other stakeholders, including donors. The Network works towards the effective use of globally available resources in providing a platform and infrastructure for the collaboration and exchange of quality and technical information. The main objective of the Network is to facilitate the access to and availability of prequalified vaccines (or other biotherapeutic products) through reliance on the batch release of the respective Network member NRAs/NCLs by recipient countries, thereby reducing redundant testing and contributing to more cost-effective testing and more effective regulatory oversight.

e) Pharmacovigilance

In the field of pharmacovigilance, the exchange and sharing of data is critical. More than 100 Member States contribute by sharing their safety data to the WHO Global database of individual case safety reports (ICSR) - VigiBase - developed and maintained by the Uppsala Monitoring Center (UMC) (30). Member States rely upon this resource (and thereby, on each-others’ data) as a single point of pharmacovigilance information, to confirm and validate signals of adverse events with medicines and vaccines that they may have observed within their own jurisdictions.

The EU introduced the concept of a supervisory authority for pharmacovigilance in 2012 in the Regulation 1235/2010 (31) who shall be responsible for verifying on behalf of the Union that the marketing authorization holder for the medicinal product satisfies the pharmacovigilance requirements as per EU legislation.

f) Inspections

In the field of inspections, governments and NRAs in different regions and parts of the world have worked on mutual recognition agreements in order to rely on each other’s inspection outcomes, avoiding the duplication of inspections and making the best use of resources, e.g. EU Mutual Recognition Agreements (32) with Australia, Canada, Japan, Switzerland and the United States of America (USA); ASEAN Mutual Recognition Agreement (33), etc.
The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a non-binding, informal co-operative arrangement between regulatory authorities in the field of Good Manufacturing and Good Distribution Practices (GMP and GDP) of medicinal products for human or veterinary use, and more recently also in Good Clinical Practices (GCP) and Good Pharmacovigilance Practices (GVP) (34). It aims at facilitating cooperation and networking between competent authorities, regional and international organizations, thus increasing mutual confidence regarding inspections. PIC/S has also issued a guidance on inspection reliance, which outlines a process for the desk-top assessment of GMP compliance (35).

Reliance is also an important aspect for conducting desktop assessment of compliance with relevant good practice guidelines and requirements, as described in the respective WHO guidance (36).

The OECD operates the Mutual Acceptance of Data system in the assessment of chemicals (including pharmaceuticals) which supports the acceptance of data, generated in any member country in accordance with OECD test guidelines and Principles of Good Laboratory Practices (GLP), in any other member country for assessment purposes relating to the protection of human health and the environment (37).

**g) Examples in the field of medical devices**

The use of reliance is equally prevalent in the regulation of medical devices including in vitro diagnostics. An example of this is the Medical Device Single Audit Program (MDSAP) (38) originally developed through the auspices of the International Medical Device Regulators Forum (IMDRF). Under this program, the regulatory authorities of Australia, Brazil, Canada, Japan and the United States have pooled their resources in order to develop and implement a robust system of oversight of third party auditing organizations that, in turn, conduct audits of the quality management systems of medical device manufacturers. The MDSAP allows an auditing organization recognized by the Program to conduct a single regulatory audit that satisfies the relevant requirements of the regulatory authorities participating in the program. Collective regulatory resources are directed at establishing and maintaining the oversight of auditing organizations, providing a more effective use of limited regulatory resources. Employing a single audit program allows regulatory authorities to efficiently leverage resources and streamline the regulatory process without compromising public health and to promote more aligned and consistent regulatory requirements.
The IMDRF has also set guidance for the exchange of information between NRAs respect to medical device safety (39). The system focuses on incidents that represent a serious public health threat that extend beyond national borders in order to inform other NRAs of such. Additionally, IMDRF outlines consistent adverse event reporting, coding, and terminology in their IMDRF terminologies for categorized Adverse Event Reporting: terms, terminology structure and codes document (40).

The above-mentioned initiative and guidance are just two examples of the work IMDRF does in the field of harmonization, convergence and reliance in the area of medical devices. Other examples are The IMDRF Optimizing Standards for Regulatory Use (41), the Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices (42) or the Competence, Training, and Conduct Requirements for Regulatory Reviewers (43).

In Singapore, medical devices and in vitro diagnostics with prior authorization through specific market authorization pathways in the United States, Europe, Canada, Australia, or Japan are eligible for abridged evaluation routes. To qualify for this, the proposed intended use must be identical to that approved in the reference country and typically documentation including proof of approval from the reference regulatory authority and summary technical documentation can be used to satisfy many supporting documentation requirements (44). Additionally, Australia will recognize registrations and certifications from Notifies bodies designated by the medical device regulators of European member states, U.S. FDA, HC, the PMDA and MDSAP auditing organizations (45).
10. References


