WHO Drug Information

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Abbreviations and websites

CHMP  Committee for Medicinal Products for Human Use (EMA)
EMA  European Medicines Agency (www.ema.europa.eu)
EU  European Union
FDA  U.S. Food and Drug Administration (www.fda.gov)
Health Canada  Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
HPRA  Health Products Regulatory Authority, Ireland (www.hpra.ie)
HSA  Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICDRA  International Conference of Drug Regulatory Authorities
ICH  International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP  International Generic Drug Regulators Programme (https://www.igdrp.com)
MHLW  Ministry of Health, Labour and Welfare, Japan
MHRA  Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe  New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int  The International Pharmacopoeia (http://apps.who.int/phint/)
PRAC  Pharmacovigilance Risk Assessment Committee (EMA)
PMDA  Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic  Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA  Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S.  United States of America
WHO  World Health Organization (www.who.int)
WHO MHP  WHO Access to Medicines and Health Products Division (www.who.int/medicines/en/)
WHO RPQ  WHO Regulation and Prequalification Department
WHO PQT  WHO Prequalification Unit (https://www.who.int/topics/prequalification/en/)
WHO HPS  WHO Health Product Policy and Standards Department

Note:  The online version of this issue (freely available at www.who.int/medicines/publications/druginformation) has
POLICY
EVALUATING AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS WHO LISTED AUTHORITIES
(December 2019)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to Mr Hiiti Sillo, Group Lead, Country Regulatory Strengthening, Regulatory Systems Strengthening Team, email: (silloh@who.int), with a copy to Yvonne Melounou (melounouy@who.int) by 28 February 2020 in the format foreseen for this purpose as per below.

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

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

This policy, and related guidelines and procedures, constitute an operational framework for WHO Listed Authorities.

This policy was developed following broad public consultation and the review of written comments received from the publication of a concept note (1) and subsequent draft policy, as well as international consultative meetings with Member States and interested stakeholders. It also considers recommendations from the Fifty-first meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Products (ECSPP) on the replacement of the term stringent regulatory authority with WHO Listed Authority (WLA). Recommendations considered comments received on the proposed elements of a replacement definition for SRA posted by WHO for public comment in August 2017 that was intended to provide a more transparent, robust and equitable measure of regulatory capacity and performance (2).

2. Context

World Health Assembly Resolution 67.20 on Regulatory system strengthening for medical products (3) recognizes that effective regulatory systems are an essential component of health system strengthening, contribute to better public health outcomes and are necessary to the implementation of universal health coverage. The Resolution 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) (4), Regional Strategy for Improving Access to Essential Medicines in the Western Pacific Region (2005-2010) (5), and document AF/RC63/7 of the WHO Regional Office for Africa (AFRO) (6). The road map for access to medicines, vaccines and other health products (WHA72/17) 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 (7).

The World Health Organization (WHO) supports countries in strengthening regulatory systems as a means of promoting equitable access to quality assured medical products. An important area of support involves the benchmarking of regulatory systems as mandated through WHA 67.20, which calls upon the WHO to apply evaluation tools to generate and analyse evidence of regulatory system performance; facilitate the formulation and implementation of institutional development plans; and provide technical support to national regulatory authorities and governments.
The benchmarking of regulatory systems referred to in WHA 67.20 implies a structured and documented process by which Member States can assess and address gaps. The Global Benchmarking Tool (GBT) represent the primary means by which the WHO evaluates regulatory systems (8).

The objectives of the WHO regulatory system strengthening program are to:

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

These measures are intended to help ensure the availability of safe, effective and quality medical products by assisting countries reach and sustain a level of regulatory oversight that is effective, efficient and transparent.

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. Regulatory cooperation and reliance are built on trust and confidence, which in turn depend on greater knowledge of regulatory systems.

The introduction of a framework for designating and publicly listing a regulatory authority as a WHO Listed Authority provides a transparent and evidence-based pathway for regulatory authorities to be globally recognized as meeting WHO and other international recognized standards and practices, replacing the concept of a stringent regulatory authority (SRA) which was initially developed to guide global procurement of medicines. The concept of a stringent regulatory authority or SRA has been used by the WHO Secretariat and the Global Fund to Fight AIDS, Tuberculosis and Malaria 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) (9) but utilization of this concept has been documented since 2003. An interim definition adopted by ECSPP in 2017 restricted eligibility to membership prior to 23 October 2015 while awaiting the development of a more suitable definition and approach based on WHO benchmarking of regulatory systems (10).

The WLA framework also replaces the concept and procedure for recognizing regulatory authorities exhibiting ‘a high level of performance’ in vaccine regulation based on criteria defined in WHO Technical Report Series (TRS) 978 (11).
While the GBT remains the foundation for assessing regulatory inputs, processes and outputs, the WLA framework is meant to provide a more detailed picture of how a regulatory system operates through an expanded performance evaluation process that examines key regulatory outputs and consistency in adherence to international standards.

The designation of a regulatory authority as a WLA is ultimately meant to promote access, supply and use of safe, effective and quality medical products.

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.

5. Policy statement

Efficient, effective 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 WHO listed authorities provides a mechanism to document and recognize well-performing regulatory systems and thereby:

- promote trust, confidence and reliance between regulatory authorities;
- encourage continuous improvement of regulatory systems and efficient use of regulatory resources;
- expand the pool of regulatory authorities contributing to the efficiency of the WHO Prequalification (PQ) programme through the increased use of abridged/streamlined procedures to PQ listing;
- promote the supply of quality assured medical products for use by UN procurement agencies and countries; and
- create an enabling environment for innovation and local production of medical products.
6. Definitions

**WHO Listed Authority (WLA)**
A national regulatory authority\(^1\) 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. A regulatory authority can be listed for one or more product categories or for one or more regulatory functions.

**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 or legal framework. The common framework must ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies. The regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework. A regional regulatory system so described may be considered a single entity and therefore eligible for listing as a WLA, as well as the individual authorities that are part of the system\(^2\).

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.

- The process to establish a WLA is initiated by a request from the Member State.
- The WHO Global Benchmarking Tool (GBT) and the performance evaluation process form the basis for evaluating the maturity level and performance of the regulatory authority against requirements established for the scope of listing being sought (product category or regulatory function).
- Regulatory authorities must at least meet requirements defined by WHO for a maturity level 3 authority to be eligible for consideration as a WLA.
- Once the WHO confirms eligibility criteria are met, the regulatory authority and WHO agree to a written plan of evaluation and commit the necessary resources to execute the plan, which may be adjusted from time to time.
- All available evidence including from previous benchmarking/audit exercises, is taken into consideration when determining compliance with the requirements for designation as a WLA. All non-public information provided is kept confidential.

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\(^1\) 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.

\(^2\) A regional regulatory system may be designated a WLA for those regulatory functions and product categories subject to a unified set of requirements, processes and set of controls.
Following the successful completion of the WLA evaluation process, a regulatory authority is publicly listed as a WHO listed authority. The listing includes the scope of the designation (product types and/or regulatory functions); evidence reviewed, and process undertaken to support the listing; and the period of validity of the listing.

A listing will normally be valid for a period of at least 5 years, provided no changes have taken place that could negatively impact the WLA listing, and that no event has taken place which could cause sufficient concern to trigger an earlier re-evaluation of the authority. An abbreviated, risk-based process will be used when re-evaluating a WLA.

To ensure impartiality of the WLA process, a recommendation to list or delist a regulatory authority is made following a review of the report of the candidate WLA evaluation team by an independent committee of experts designated by WHO based on established and transparent criteria. The review process, as described in the operational guidance, provides an additional level of assurance that due process was followed, and that decisions are supported by findings.

WHO reserves the right to delist a regulatory system should, upon evaluation and subsequent discussion with the regulatory authority, it is concluded that the basis for supporting the listing is no longer valid. Delisting and the rationale for delisting are made public. The decision to delist would follow a meeting with the regulatory authority during which the authority would have an opportunity to present its case.

The designation of WLAs is meant to substantiate the maturity and performance of regulatory authorities using an international benchmark, as defined by the GBT and the performance evaluation process. It is not meant to make any inference regarding the maturity or performance of a regulatory authority that has not been evaluated by WHO.
References

1. Working document QAS/19.808, May 2019
   (https://www.who.int/medicine/areas/quality_safety/quality_assurance/qas19_808_WHO_listed_authorities.pdf?ua=1)

2. Working document QAS/17.728/Rev.1, August 2017
   (https://www.who.int/medicine/areas/quality_safety/quality_assurance/SRA_QAS17-728Rev1_31082017.pdf?ua=1)

3. WHA Resolution 67.20, 24 May 2014
   (https://apps.who.int/mediacentre/documents/s21456en/s21456en.pdf)

4. Resolution CD 50.R9, 27 September – 1 October 2010


6. AFR/RC63/7, 3 September 2013

7. WHA Resolution 72/17, 4 April 2019

8. WHO Global Benchmarking Tool
   https://www.who.int/medicine/regulation/benchmarking_tool/en/


10. WHO TSR 1003, October 2017, pages 34-35
    (https://apps.who.int/iris/bitstream/handle/10665/258720/9789241210034-eng.pdf?sequence=1&isAllowed=y&ua=1)

11. WHO TSR 978, 2013, Annex 6
    (https://www.who.int/biologicals/expert_committee/TRS_978_61st_report.pdf?ua=1)
Annex 1

Maturity level

Maturity level represents an estimation of the effectiveness and performance of a regulatory system or regulatory function as graded on a scale, based on an evaluation of the legal framework, regulations and guidelines; regulatory practices and procedures; organizational structure; management and administration; and human resource capacity and development. WHO has classified regulatory systems and functions on a scale from 1 to 4.

ML 3 represents the baseline set by WHO for a well-functioning regulatory system based on international standards and good regulatory practices. WHO recognizes that it may not be realistic for some Member States to achieve ML 3, for example, in the case of low resourced member states. In such situations, efforts should be focused on establishing essential, value-added regulatory functions while relying on other reference regulatory authorities, international organizations and/or as part of a common regulatory network for providing assurance of the quality and safety of supplied medical products.

The GBT is designed to provide a robust and structured approach to analysing the required inputs (legal framework, organizational structure and resources), regulatory processes and intended outputs that together determine how well a regulatory authority is configured to ensure the safety, efficacy and quality of medical products in an effective, transparent manner. While the benchmarking tool contains indicators to measure performance, the extent of measurement is limited by the duration of benchmarking missions. The WLA performance evaluation process supplements and expands the assessment of key regulatory outputs in order to provide a more detailed picture of how a regulatory system operates.
Regulatory System Maturity Level

1. **No formal approach**
   - Some elements of regulatory system exist

2. **Reactive approach**
   - Evolving national regulatory system that partially performs essential regulatory functions

3. **Stable formal system approach**
   - Stable, well-functioning and integrated regulatory system

4. **Continual improvement emphasized**
   - Regulatory system operating at advanced level of performance and continuous improvement

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REVISION OF WHO GMP FOR STERILE PHARMACEUTICAL PRODUCTS – A JOINT EU, PIC/S, WHO PROJECT

(February 2020)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document 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) by 20 April 2020 in the format foreseen for this purpose as per below.

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

If you wish to receive our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.
REVISION OF WHO GMP FOR STERILE PHARMACEUTICAL PRODUCTS
A JOINT EU, PIC/S, WHO PROJECT

As a follow-up to the recommendation of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECOSPP), the WHO Secretariat actively pursues its efforts towards an efficient collaboration with the European Union (EU) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) in the revision process of the good manufacturing practices (GMP) for sterile products: WHO Good Manufacturing Practices for Sterile Pharmaceutical Products:

It is viewed that a common language would be beneficial to the authorities and the manufacturers, save resources and, thus, would ultimately benefit patients in having better access to quality medicines.

The manufacture of sterile medical products covers a wide range of product types (sterile active substance through to finished dosage form), batch sizes (single unit to multiple units), processes (from highly automated systems to manual processes), primary packaging materials and technologies (e.g. biotechnology, classical small molecule manufacturing and closed systems). This Annex provides general guidance that should be used for all sterile medical products and sterile active substances, via adaption, using the principles of quality risk management (QRM) to ensure that microbial, particulate and pyrogen contamination associated with microbes is prevented in the final product.

In order to maintain the global alignment of standards, achieving at the same time assurance for the highest quality, the document will be, in parallel, subject to a second joint targeted consultation by the European Commission (EC)/European Medicines Agency (EMA), WHO and PIC/S.
**Objective of the consultation**

This revision is intended (i) to add clarity, (ii) introduce the principles of QRM to allow for the inclusion of new technologies and innovative processes and (iii) to change the structure to a more logical flow. Key changes are as follows:

- Introduction of new sections;
- Introduction of QRM principles;
- Restructured to give more logical flow; and
- Added detail to a number of the previous sections to provide further clarity.

A first consultation, conducted from 20 December 2017 to 20 March 2018, allowed approximately 140 companies and/or organizations to comment. The joint PIC/S-EMA drafting group (with WHO participation) processed more than 6 200 lines of comments.

Due to widespread interest from industry following the first consultation, and because of substantial modifications introduced in several sections, the EC, EMA, WHO and PIC/S have agreed to engage a second consultation with stakeholders on the updated draft guidance (version 12) focusing on the sections and/or significantly modified paragraphs that raised the most concerns from stakeholders.

The second consultation aims to gather experience from the sectors on certain manufacturing steps. It is expected to receive contribution from the associations representing the sectors.

There are two options in sending feedback to this new draft document:

1. **VIA THE TARGETED STAKEHOLDERS’ CONSULTATION PROCESS COORDINATED BY THE EU**

   **Period of consultation**

   From 20 February to 20 May 2020.
How to submit a contribution

Comments will be collected by the EC directly, as well as a number of organisations representing relevant stakeholders who have agreed to receive all the comments from their members, to compile and send the comments to the EC. For the list of stakeholders, please refer to the EC’s website (link provided below), in particular to the section on “Targeted Stakeholders”.

To download the consultation document and the template required to submit comments, as well as the process on how submit comments, please refer to the EC’s website using this link: https://ec.europa.eu/health/medicinal_products/consultations/2020_stereile_medicinal_products_en and “How to submit a contribution”.

Contact details

Responsible service:
Health and Food Safety Directorate General
Unit B4 - Medicinal products: quality, safety, innovation

Any queries about the public consultation should be sent to: SANTE-REVISION-OF-ANNEX-1@ec.europa.eu.

2. DIRECTLY TO THE WHO SECRETARIAT

Period of consultation

From 20 February to 20 April 2020.

Objective of the consultation

As an opportunity for convergence in the area of GMP, WHO is once again widely circulating the new proposal, developed by EU and PIC/S with input from WHO, in order to obtain feedback and comments on the revision following the first joint consultation in December 2017 and a review of the more than 6 200 comments by the drafting group. The proposal is to replace the text WHO Good Manufacturing Practices for Sterile Pharmaceutical Products published as Annex 6, WHO Technical Report Series, No. 961, 2011, with the text of the newly revised “EU-PIC/S GMP Annex 1 on the Manufacture of Sterile Medicinal Products”. 
How to submit a contribution

Please send any comments you may have on the attached revision to Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals (kopps@who.int) with a copy to Ms Claire Vogel (vogelc@who.int) by 20 April 2020 in the format foreseen.


It has been formatted with prescribed line and page numbers in order to support a joint international consultation with the EC, PIC/S and WHO.

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