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 EMP  WHO Essential medicines and health products (www.who.int/medicines/en/)
WHO PQT  WHO Prequalification team (https://extranet.who.int/prequal/)

Note: The online version of this issue (freely available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and websites referenced
Publication News


The WHO ECSPP advises the Director-General of WHO in the area of medicines quality assurance. The Expert Committee oversees the maintenance of The International Pharmacopoeia and provides guidance for use by relevant WHO units and regulatory authorities in WHO Member States, to ensure that medicines meet unified standards of quality, safety and efficacy. The Expert Committee’s guidance documents are developed through a broad consensus-building process, including an iterative public consultation phase. Representatives from international organizations, state actors, non-state actors, pharmacopoeias and relevant WHO departments are invited to the Expert Committee’s annual meetings, to provide updates and input to the Committee’s discussions.

At its 53rd meeting held from 22 to 26 October 2018 in Geneva, Switzerland, the Expert Committee heard updates on cross-cutting issues from other WHO bodies, including the ECBS, the Expert Committee on the Selection and Use of Essential Medicines, local manufacturing, the programme working to combat AMR, the Member State mechanism on substandard and falsified medical products, the INN programme and the RSS unit. Updates were also presented by partner organizations, including UNICEF and the PDG and by the IAEA.

Progress updates on quality control activities were presented by the EDQM as the custodian centre in charge of ICRS for use with monographs of The International Pharmacopoeia. Briefings were also provided on the outcomes of the Ninth International Meeting of World Pharmacopoeias, which was co-hosted by WHO and Viet Nam, and on the results of proficiency testing studies conducted in Phase 8 of the WHO EQAAS.

Progress updates were provided on prequalification of medicines, APIs and quality control laboratories, and on completed and planned surveys to monitor the quality of medicines circulating on the markets of Member States.

The Expert Committee reviewed new and revised specifications and general texts for quality control testing of medicines for inclusion in The International Pharmacopoeia (1). The Expert Committee adopted 9 guidelines and 12 pharmacopoeial texts (2 general chapters, 10 new and revised monographs), and confirmed the release of 8 new ICRS established by the custodian centre for ICRS and two for use in connection with The International Pharmacopoeia.
The decisions and recommendations made by the Expert Committee at its 53rd meeting in 2018 are listed next.

**The following guidelines and decisions were adopted and recommended for use:**

- *Procedure for the development of World Health Organization medicines quality assurance guidelines* (Annex 1) *(new)*
- *Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products* (Annex 2) *(new)*
- *Good manufacturing practice: guidelines on validation:*
  - General main text (Annex 3) *(revision)*
  - *Analytical procedure validation* (Annex 3 – Appendix 4) *(revision)*
  - *Validation of computerized systems* (Annex 3 – Appendix 5) *(revision)*
  - *Guidelines on qualification* (Annex 3 – Appendix 6) *(revision)*
- Proposal to waive in vivo bioequivalence requirements for medicines included in the EML – set of priorities agreed
- Pilot study 3 of new API data and classifications confirmed
- *Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (Annex 4) *(new)*
- *Guidelines on import procedures for medical products* (Annex 5) *(revision)*
- *Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products* (Annex 6) *(new)*

**For inclusion in The International Pharmacopoeia**
The following general texts were adopted by the Expert Committee:
- Workplan 2018–2019

**General chapters**

- 2.2.3 Limit test for heavy metals *(revision)*
- 5.5 Dissolution test for solid oral dosage forms *(revision)*

**Monographs**

*For medicines for maternal, newborn, child and adolescent health*

- estradiol valerate
- ethinylestradiol

*For antituberculosis medicines*

- moxifloxacin hydrochloride
- moxifloxacin tablets

*For antiviral medicines, including antiretroviral medicines*

- daclatasvir dihydrochloride
- daclatasvir tablets
For medicines for tropical diseases
- albendazole (revision)
- ivermectin
- ivermectin tablets

For ophthalmological and dermatological medicines
- Tetracycline hydrochloride (revision)

International Chemical Reference Substances
The Expert Committee confirmed the release of the following ICRS that have been newly characterized by the EDQM, the custodian centre:
- trimethoprim ICRS 2
- mebendazole ICRS 2
- sulfamethoxazole ICRS 2
- capreomycin sulfate for identification ICRS 1
- cycloserine ICRS 1
- methylthioniunium chloride ICRS 1
- ritonavir ICRS 3
- clindamycin hydrochloride ICRS 1.

The Expert Committee also authorized the following reference substances, established by the EDQM for use according to the respective monographs in *The International Pharmacopoeia*.
- moxifloxacin for system suitability CRS
- albendazole for system suitability CRS

Recommendations
The Expert Committee made the recommendations listed below in the various QA-related areas. Progress on the suggested actions will be reported to the Expert Committee at its 54th meeting in October 2019.

The Committee recommended that the Secretariat, in collaboration with experts as appropriate, should take the actions listed next.

The *International Pharmacopoeia*
- Continue development of monographs, general methods and texts and general supplementary information, including radiopharmaceutical monographs developed by the IAEA, in accordance with the workplan and as decided at the meeting

Quality control – national laboratories
- Continue offering the EQAAS, including to those laboratories participating in the prequalification process
Good manufacturing practices and related areas

• Develop a revised text for the “cleaning validation”, to bring it in line with new developments
• Develop a new comprehensive text on Good distribution practices, including the elements of WHO Good storage practices and other related guidance texts, such as the Guidelines for inspection of drug distribution channels
• Revision of the text on Quality system requirements for national GMP inspectorates
• Develop a document, e.g. as “points to consider”, on environmental aspects relating to manufacturing for the prevention of AMR, to possibly include the role of inspectors
• For water for injection: update the current monograph in The International Pharmacopoeia on WFI and the related GMP text, to allow other technologies for production of WFI in addition to distillation
• Develop a new text on Good chromatography practices

Distribution

• Initiate the development of new guidance on the determination of shelf-life requirements for the supply and procurement of medicines

Regulatory mechanisms

• Continue the updating process for the WHO certification scheme on the quality of pharmaceutical products moving in international commerce, with a subgroup and active involvement of Member States
• Continue the drafting of the new guidance document to support and facilitate the implementation of quality management systems for national regulatory authorities
• Continue the development of good regulatory practices
• Start the next phase of the WHO Biowaiver Project, on the BCS- based classification of the second set of APIs from the EML, in accordance with the newly adopted criteria for setting priorities, using the regulatory and experimental pathways
• Update the listing of stability conditions required for marketing authorizations in WHO Member States

Other

• Update the WHO/UNFPA guidance texts serving the prequalification of condoms, in close collaboration with colleagues in WHO and UNFPA
• Continue the revision of the Guidance on representation of graphic formulae for medicines
• Continue to provide the database of terms and definitions covered by this Expert Committee on the WHO website.
CONCEPT NOTE: A FRAMEWORK FOR EVALUATING
AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS
WHO-LISTED AUTHORITIES

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to nra_admin@who.int, with a copy to
Ms Claire Vogel (vogelc@who.int) by 17 July 2019.

Medicines Quality Assurance working documents will be sent out electronically only. They will
also be placed on the Medicines website for comment under “Current projects”.

If you have not already received our draft working documents, please send your email address
(jonessi@who.int) and we will add you to our electronic mailing list.
CONCEPT NOTE: A FRAMEWORK FOR EVALUATING AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS WHO-LISTED AUTHORITIES

1. SUMMARY

This concept note outlines a proposed framework for evaluating and publicly designating regulatory authorities as ‘WHO-listed authorities’, following upon recommendations from the Fifty-first meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Products (ECSPP) in October 2017 on the replacement of the term stringent regulatory authority with WHO-Listed Authority (WLA).

This concept note presents a proposed definition for WLA; procedures for designating a WLA; and the process for finalizing the definition and the procedures for putting the framework into place. This concept note is meant to provide sufficient information to solicit comments on proposals presented herein, not to provide details of how the framework might be implemented.

WHO intends to publish a draft WLA policy document similar in scope to this note by the end of July 2019 and draft operational guidance documents by the end of August 2019 to enable implementation of the WLA framework. Both the WLA policy document and operational guidance documents will be published for public comment.

Given the wide interest in and implications associated with the definition and framework, WHO will adopt a multi-prong consultation process as outlined in this concept note. The definition for WLA will also need to be reviewed by WHO Expert Committees1 in the context of its usage in place of stringent regulatory authority in existing WHO guidelines.

It is expected that the introduction of the WLA framework will begin with a pilot phase in the first quarter of 2020.

1 Expert Committee on Specification for Pharmaceutical Preparations (ECSPP) for the approval of the definition, consulting the Expert Committee on Biological Standardization (ECBS) to cover all product streams including vaccines and biotherapeutic products.
2. BACKGROUND

The concept of a stringent regulatory authority or SRA was developed by the WHO Secretariat and the Global Fund to Fight AIDS, Tuberculosis and Malaria to guide medicine procurement decisions and is now widely recognized by the international regulatory and procurement community. Since its introduction, the term and corresponding definition have been incorporated in the quality assurance policies of most international organizations involved in the purchase and supply of medicines, the assumption being that products assessed and approved to enter the market by an SRA would consistently meet international requirements for safety, efficacy and quality. The concept has additionally served to promote reliance on the product evaluations and decisions of SRAs by other authorities when making their own regulatory decisions.

WHO prequalification procedures and several other WHO guidance documents relating to the quality of medicines provide mechanisms to rely on SRAs, defining an SRA as a regulatory authority which is a member or an observer of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), or is associated with an ICH member through a legally binding mutual recognition agreement.

In recent years, however, there have been increasing calls for a change in the term and definition given the inference regarding other authorities; the expansion of ICH membership, as well as the fact that ICH is a harmonization initiative and does not have the mandate to assess regulatory capacity; as well as the interest of other regulators to be considered an ‘SRA’.

A subsequent, interim definition was proposed by WHO and adopted in October 2017 by the ECSPP while WHO formulated a proposal for a more suitable term and definition. The interim definition essentially maintained the original definition based on the pre-reform membership of ICH.

A proposal on the elements of a replacement definition for SRA was posted by WHO for public comment in July 2017 that was intended to provide a more transparent, robust and equitable measure of regulatory capacity and performance. The proposal set out a number of principles by which “stringent” regulatory authorities would qualify to be “on a list” established by WHO based on a formal assessment by WHO using the Global Benchmarking Tool (GBT) against requirements established for maturity level 4 (ML 4), a level which corresponds to a regulatory system operating at advanced level of performance and continuous improvement.

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2 This concern led to a recommendation at the Seventeenth International Conference of Drug Regulatory Authorities (ICDRA) on ‘moving away from using the term stringent national regulatory authority.’
The proposal also provided for a modular approach that would allow regulatory authorities to be designated as ML 4 for a specific regulatory function (such as inspection) or product group (such as the vaccine program).

Following review of public comments, the ECSPP recommended that:

- the term SRA be replaced by the term WHO-Listed Authority (WLA);
- regulatory authorities currently identified as SRAs be regarded as WHO-listed authorities;
- the designation of additional national regulatory authorities (NRAs) as WLAs be based on an assessment using the GBT, and a “performance verification process” to confirm consistency of performance against international standards and best practices; and
- the procedure for listing WLAs be developed through WHO’s public consultation process.

A similar concept of authorities exhibiting ‘a high level of performance’ was endorsed by the WHO Expert Committee on Biological Standardization (ECBS) at its Sixty-first meeting (in October 2010) within the context of streamlining the prequalification process for vaccines. The procedure for selecting eligible regulatory authorities was based on experience gained by WHO in the evaluation of influenza H1N1 (2009) pandemic vaccines. The procedure was meant to serve as an interim measure pending the development of a revised NRA assessment tool with additional performance indicators that would be able to distinguish levels of regulatory functionality (maturity levels) and performance. This now translates into the GBT and the proposed performance evaluation framework.

The harmonized medicines and vaccines GBT and the concept of categorizing regulatory authorities based on maturity level were introduced in 2016 (see Annex 1). The GBT builds upon previous regulatory system benchmarking tools used within the WHO family beginning in 1997 and also takes into account regulatory system evaluation tools used by organizations external to the WHO. The benchmarking of regulatory authorities serves as a basis for formulating institutional development plans and implementing recommended improvements.

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4 The WHO had previously introduced the concept of classifying regulatory systems according to “maturity level” following a series of international consultations and adaptations of International Standard ISO 9004 and the Benchmarking of European Medicines Agencies (BEMA) initiative.
5 For further information on the official GBT (Revision VI), please refer to the following link: [https://www.who.int/medicines/regulation/benchmarking_tool/en/](https://www.who.int/medicines/regulation/benchmarking_tool/en/) which presents the complete listing of GBT indicators and fact sheets according to regulatory functions and overarching system. A revised draft user manual will also be posted in the near future.
The goal of regulatory system strengthening is ultimately to promote access to quality assured medical products, consistent with the United Nations (UN) Sustainable Development Goal (SDG) 3\textsuperscript{6}, World Health Assembly Resolution (WHA) 67.20 on *Regulatory system strengthening for medical products*\textsuperscript{7} and the Access Roadmap\textsuperscript{8}.

This concept note presents a proposed framework for using the evaluation tool (GBT) to generate and analyse evidence of regulatory system performance, as mandated by WHA Resolution 67.20, to allow for the public listing of regulatory authorities as WLAs. Given the implications associated with the proposed change in definition and approach, WHO is seeking feedback from Member States and all interested parties through a public consultation process.

Details on the implementation of this framework will be guided by input received.

### 3. PURPOSE

The purpose of this concept note is to:

- present a proposed definition for WLA;
- define the proposed process and timelines for designating a regulatory authority as a WLA;
- describe the proposed process and timelines for finalizing the definition and the procedures for evaluating and designating and re-designating a WLA.

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\textsuperscript{6} SDG 3: ‘healthy lives and promoting the well-being at all ages…including [through]… access to safe, effective, quality and affordable essential medicines and vaccines for all.’

\textsuperscript{7} WHA Resolution 67.20 provides WHO the mandate to apply evaluation tools to generate and analyze evidence of regulatory system performance and facilitate the formulation and implementation of institutional development plans.

\textsuperscript{8} 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), Regional Strategy for Improving Access to Essential Medicines in the Western Pacific Region (2005-2010), and document AF/RC63/7 of the WHO Regional Office for Africa (AFRO).

\textsuperscript{9} 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.
The designation of a regulatory authority as a WLA is ultimately meant to promote access, supply and the intended use of safe, effective and quality medicines and vaccines by:

- providing a robust and transparent framework to promote trust, confidence and reliance between regulatory authorities and thereby enable the efficient use of regulatory resources;
- providing a pathway for regulatory authorities to be globally recognized as meeting WHO and other international recognized standards and practices and thereby help guide international and national procurement decisions on medical products, including for products not eligible for prequalification;
- increasing the pool of regulatory authorities contributing to the efficiency of the WHO Prequalification (PQ) program through the increased use of abridged procedure or alternative pathways to PQ listing;\(^\text{10}\)
- promoting investments in, and the continuous improvement of, regulatory systems;
- creating an enabling regulatory environment for innovation and local production; and
- helping contribute to regulatory collaboration and capacity building efforts and more effective global regulatory oversight of medical products.

4. DEFINITIONS

WHO proposes to publicly list regulatory authorities that satisfy the requirements for designation as WLA, as defined below:

**Maturity level 3 WHO listed authority (ML 3 WLA)**

A regulatory authority\(^\text{11}\) which has been documented to comply with all of the indicators and requirements specified by WHO for maturity level 3 based on an established benchmarking process.

Represents a stable, well-functioning and integrated regulatory system.

\(^\text{10}\) Regulatory networks are increasingly important in building capacity and promoting convergence, harmonization, work-sharing and reliance. This in turn should result in greater regulatory efficiencies, effectiveness and transparency of operations. WHO also intends to take greater advantage of joint assessments and inspections performed by regulatory networks in the PQ process. Details on how this alternative PQ listing process will operate will be described in a separate document.

\(^\text{11}\) 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.
Maturity level 4 WHO listed authority (ML 4 WLA)

A regulatory authority which has been documented to comply with all of the indicators and requirements specified by WHO for maturity level 4 and to consistently adhere to WHO and other internationally recognized standards based on an established benchmarking and enhanced performance evaluation process.

Represents a regulatory system operating at an advanced level of performance and continuous improvement, currently known as a stringent regulatory authority (medicines) and an authority exhibiting ‘a high level of performance’ (vaccines).

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. 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.

Note: A regional regulatory system may be designated a WLA for those regulatory functions subject to a unified set of requirements, processes and set of controls. At present, the GBT is designed to evaluate national regulatory systems. The WHO is in the process of developing a system for evaluating the performance of regional regulatory networks or systems.

Maturity level (ML)

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 12.

See Annex 1 for further details on maturity levels as they relate to the classification of authorities responsible for the regulation of medical products.

12 Adapted from ISO and BEMA definitions.
In the initial implementation phase of the WLA framework, a regulatory authority may be designated a WLA for the regulation of generic medicines, for new medicines, and/or for vaccines, reflecting the current scope of the WHO benchmarking program. The scope of program and listing options will gradually expand, beginning with medical devices (including in-vitro diagnostics) and blood and blood products.

A regulatory authority may also be designated a WLA for one or more regulatory functions such as inspection. In all cases, the listing would specify the scope of designation (see Annex 2).

In situations where the regulatory system is divided across different levels within the country, for example central/national and provincial/state/municipal entities, the initial designation as a WLA may be restricted to central and certain provinces and states, taking into consideration the size and administrative complexity of the country.

The principal difference between the designation of ML 3 and ML 4 WLAs relates to the fact that:

i. an ML 4 WLA must comply with ML 4 indicators relevant for the designation being sought; and

ii. the performance, that is, the ability of the regulatory authority to consistently adhere to international standards and best practices, has been more fully evaluated and documented.

The designation of WLAs is meant to substantiate the maturity and performance of regulatory authorities using an international benchmark, as defined in the GBT. It is not meant to make any inference regarding the maturity or performance of regulatory authorities that have not been evaluated by WHO under the proposed framework.

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14 It is important to note that an ML 3 WLA must comply with all the GBT indicators specified for a ML 3 regulatory system for medicines and/or vaccines, as documented by a formal benchmarking by WHO. This means that the authority must meet indicators for ML 1 to ML 3, inclusively. An ML 4 WLA must additionally comply with relevant ML 4 indicators specified for the scope of listing being sought, for example, generic medicines program or regulatory inspection. Further details will be available with the publication of the draft GBT manual, including with respect to the scoring of indicators, later in 2019.
Similarly, while the performance of ML 3 WLAs will not be evaluated to the same level as for agencies seeking ML 4 WLA designation, the same considerations stated above apply. It is also important to recognize the significance of attaining ML 3, the objective of WHO regulatory system strengthening efforts for most countries, and of WHA Resolution 67.20, representing an international baseline for effective regulation.

As per current practice, a regulatory authority that complies with ML 3 requirements for vaccines satisfies a prerequisite for application by vaccine manufacturers in that country to the WHO PQ program.

5. PROCESS FOR APPLICATION, EVALUATION AND LISTING AS A WLA

A written application must be submitted to WHO from the regulatory authority requesting WLA listing that would include the authority’s agreement with the general evaluation methodology, the obligations of the regulatory authority throughout and following the process, and the publication of the outcome (the listing) and a summary basis of the decision on the WHO website. The authority is encouraged to meet with the WHO Secretariat to discuss the WLA evaluation and listing process prior to the formal application process.

Regulatory authorities applying for listing should have an established history of interaction with WHO (see below) and be in a position to comply with the requirements for listing within a reasonable period of time. This will be considered by WHO in the application evaluation step. As each regulator and situation is unique, WHO will work with the authority to establish a roadmap to reach a listing decision.

Should it become evident during the course of the combined benchmarking-performance evaluation exercise that the regulatory authority is unlikely to meet requirements for listing within a 6 – 12-month timeframe from the start of the benchmarking-evaluation process, depending on the scope of designation, the authority would be invited to reapply at a later time once identified areas for improvement have been addressed.

Upon successful review of the application, the WHO Secretariat will meet with the regulatory authority to discuss and agree upon a roadmap for the WLA evaluation process that considers the scope of designation requested, the state of readiness of the authority and WHO, and all available information supporting the maturity and performance level of the authority.

15 Does not apply to transitional arrangements referred to on page 11.
Depending on the number of requests, WHO may prioritize eligible requests based on the estimated impact on the regional or global supply of quality assured medicines or vaccines.

The listing on the WHO website would specify the product categories (generic and/or new medicines and/or vaccines) or regulatory functions (such as regulatory inspection) for which the designation applies (see Listing Process below).

The scope of listing for WLA product centric regulatory programs - generic medicines, new medicines and vaccines - includes the overarching regulatory system and all functions related to the regulatory oversight of the products that are within the scope of the program.

With a view to encouraging incremental investment in regulatory systems and the attainment of an international level of capacity and performance, regulatory authorities would also be eligible to apply for listing in a regulatory function defined by the GBT, such as regulatory inspection, marketing authorization, laboratory testing or vigilance (see Annex 2).

6. CONSIDERATIONS IN THE DESIGNATION AND LISTING PROCESS

- It is essential that the outcome (listing decision) and summary basis for the listing decision be made public in order to have the intended impact in promoting trust, reliance, sound procurement decisions and investments in regulatory systems.

- Related to this point, regulatory authorities, procurement agencies and other stakeholders must have confidence in the process and outcomes. This means that WLA authorities must be recognized as complying with robust standards for evaluating regulatory systems, as developed with the input of experts from regulatory authorities and as published on the WHO website.

- All available evidence and outcomes, including from previous benchmarking/audit exercises, will be taken into consideration when determining compliance with the requirements for designation as a WLA.

- WHO supports the practice of reliance and recognition by even the most advanced and resourced regulatory authorities as a means of addressing the complexities of the global regulatory environment and promoting effective use of resources. A WLA authority, however, is expected to have the capacity to perform all regulatory functions related to medicine and/or vaccine regulation.
7. PERFORMANCE EVALUATION PROCESS

WHO will take account of all existing evidence supportive of adherence to international standards and best practices to expedite the performance evaluation process, including WHO’s experience interacting with the regulatory authority.

The performance evaluation activity is expected to provide a more detailed picture of how a regulatory system operates. It should serve to document consistency in adherence to procedures and in producing outputs which are consistent with the application of WHO and other international regulatory requirements and best practices. The framework will consider the nature and extent of evaluation required to provide a high degree of confidence in the authority’s performance.

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.

The benchmarking process requires independent experts to gather and review evidence described in fact sheets for all GBT indicators in order to document the level of implementation of a particular regulatory function, for example, regulations and guidelines for market authorization that define the types and scope of product variations and the required documentation for each type of variation.

In finalizing the current version of the GBT, performance indicators and the accompanying instructions on evidence to collect and review were elaborated for many of the regulatory functions. For example, in relation to Registration and Market Authorization (MA):

**MA01.09: Specific guidelines on the quality, nonclinical and clinical aspects are established and implemented:**

**Evidence to review:**

- *Examples of MA application submissions that are in compliance with the published guidelines.*

- *Evidence that documents submitted were appropriate for the type of product and type of application.*

- *Copies of all quality, safety, efficacy reports for recently approved MA applications to determine whether reviews were done thoroughly and based on guideline requirements.*
While the GBT is designed to measure the existence and level of implementation of inputs and processes against specified indicators, as well as the performance of the regulatory system - that is, how the component inputs and processes result in desired regulatory outputs - the challenge has been the time required to fully evaluate the consistent performance during a formal benchmarking mission.

WHO intends to address this challenge through an expansion of performance measurement within the overall benchmarking process. Performance measurement would be more comprehensive in relation to a ML 4 thereby providing a more detailed evaluation of regulatory outputs over a defined period of time or number of regulatory activity units, such as product assessment, good manufacturing practice (GMP) inspection or laboratory analysis.

Figure 1 - Standard benchmarking process
The development of the performance evaluation framework will be guided by comments received and draw upon similar frameworks developed to establish performance and equivalence between regulatory systems. The framework will also take into consideration experience gained from evaluations of performance currently conducted by WHO, for example, in relation to GMP inspection and the management of adverse events following immunization (AEFI) for vaccine programs. It will also provide an opportunity to pilot the WHO global competency framework for evaluating human resource capacity and development.16

WHO will assemble a group of regulatory experts to assist in developing the performance evaluation framework.

As the performance evaluation exercise will require investment in resources on the part of the regulatory authority and WHO, authorities applying for listing should be in a position to complete the process within 6-12 months from the start of the integrated benchmarking-performance evaluation process, depending on the scope of the evaluation.

8. LISTING PROCESS

Following the successful completion of the WLA evaluation process, a regulatory authority will be listed on the WHO website. To bring further impartiality to the process, it is proposed that a recommendation to list a regulatory authority be made following a review by an independent committee of experts designated by WHO based on the report and recommendation from the evaluation team17.

The listing would indicate the scope of the designation, for example, generic medicines, vaccines or pharmacovigilance as well as the maturity level of the authority. The period of validity of the listing would also be indicated (see below).

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16 Human resource constraints have been identified as a challenge for regulatory systems globally, especially in low- and middle-income countries (LMICs), impacting on access to quality, safe and efficacious medical products in those settings. The Institute of Medicine (IOM) report *Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad* identified the current ad hoc and inconsistent trainings offered to LMICs as part of the problem. While WHO has established a well-recognized process for benchmarking and strengthening regulatory systems, there is a growing recognition that the current approach in regulatory capacity development must include a common global competency framework to achieve the desired public health outcomes.

17 The terms of reference and composition of the review committee are under development.
The list would be accompanied by summary information, including:

- an outline of the organizational structure and responsibilities of the regulatory system evaluated;
- evidence reviewed, and the process undertaken to support the listing;
- scoring (overall percentage of indicators met) and maturity level per regulatory function (see Annex 3);
- a summary of recommendations on further improvement; and
- a link to relevant website/webpages of the regulatory authority.

It may also include additional information, for example, regarding the pharmaceutical profile of the country.

Full details of the evaluation are available to the regulatory authority in question. Regulatory authorities are free to share any information related to the evaluation with other parties.

9. RENEWALS AND VALIDITY PERIOD

Renewal of listing would be based on a risk-based re-evaluation process that takes into consideration the fact that WLA authorities should be in a state of continual improvement. Typically, re-evaluation would involve a desk-based review by WHO appointed regulatory experts supplemented, if required, by on-site evaluation. The re-evaluation would be based on a self-assessment by the authority.

Additionally, WLAs would be required to confirm on a periodic basis\textsuperscript{18}, or as appropriate, that no changes have taken place that could negatively impact the WLA listing, in addition to any significant developments that should be reflected in updated summary information published on the WHO website.

A validity period of seven (7) years is proposed for ML 3 WLAs, provided no changes have taken place that could negatively impact the WLA listing. Following the initial evaluation by WHO, it is proposed that ML 4 WLAs would not be subject to subsequent re-evaluation in relation to the program or regulatory function listed as ML 4, provided that no event has taken place which could cause concern and trigger a re-evaluation of the authority. WHO nonetheless reserves the right to conduct a re-evaluation of an authority based on concerns related to the continued validity of evidence supporting WLA designation (see below).

\textsuperscript{18} To be defined in operational guidance.
This approach takes into account the fact that these regulatory systems may be considered the most advanced and transparent, with continual improvement processes in place. In all cases, reporting requirements described above apply.

Consistent with the above, WHO will continue to adopt a risk-based approach that devotes greater resources and effort to strengthening less mature systems, taking into account the potential impact on the production and supply of quality assured medical products.

10. DELISTING

Similar to the practice established by the WHO PQ program in relation to the delisting of prequalified products, WHO reserves the right to delist a regulatory system should, upon evaluation and subsequent discussion with the regulatory authority, WHO concludes that the basis for supporting the listing is no longer valid. This could be due to evidence of serious and persistent lapses in regulatory oversight, ineffective enforcement activities, a major downsizing or re-organization of the authority, or a lack of response to requests for re-evaluation. It could also be a result of the voluntary decision of the regulatory authority.

The decision to delist would be made based on a recommendation from the WHO independent review committee of experts\(^{19}\) following a meeting with the regulatory authority, during which the authority would have an opportunity to present its case.

Should a delisting occur, the authority would be provided the basis for the decision, which would then be made public. The authority would be permitted to reapply for listing based on an agreed corrective action plan and a possible re-benchmarking by WHO.

11. TRANSITIONAL ARRANGEMENTS

Transitional arrangements are proposed to ensure that the introduction of the listing process does not disrupt the supply of prequalified and other quality assured medical products for purchase by UN agencies and countries. Arrangements also take in consideration ECSPP recommendations and evidence already available to the WHO.

Regulatory authorities identified as SRAs\(^{20}\) for medicines regulation by the current interim definition will be entered onto the list of ML 4 WLAs for a period of five years as of the date the WLA framework comes into effect. The same would apply to regulatory authorities that comply with the requirements of Technical Report Series (TRS) 978 (Annex 6) in relation to vaccines regulation.

\(^{19}\) The same committee involved in the recommendation to list the WLA.

\(^{20}\) For the purpose of transitional arrangements, SRA within the context of the European Union (EU), applies to market authorisations granted through centralised, decentralised or mutual recognition procedures.
National Regulatory Authorities of Regional Reference (NRArr)\textsuperscript{21} evaluated by Pan American Health Organization (PAHO/WHO) within the last three (3) years from the effective date of the WLA framework will be entered onto the list as ML 3 WLAs for a period of five (5) years.

During this period, WHO will work with the above authorities at their request to develop a plan for documenting their maturity and performance as a pre-requisite to re-listing. All available supporting evidence would be considered in developing the plan and could include a desk-based assessment performed by a team of peers under the direction of WHO against the GBT performance evaluation framework using information in the public domain whenever possible\textsuperscript{22}.

The plan for relisting of an NRArr could target ML 4 at the request of the regulatory authority based on the previous benchmarking by PAHO/WHO and a gap analysis against the GBT (Revision VI).

Similarly, for authorities that have been formally benchmarked since 2016 using the previous version of the GBT (Revision V) and found compliant with indicators for ML 3, a gap analysis against GBT (Revision VI) would form the basis for developing a plan for listing.

12. PROCESS AND TIMELINES FOR FINALIZING THE DEFINITION AND THE PROCEDURES FOR EVALUATING AND DESIGNATING A WHO-LISTED AUTHORITY

WHO intends to complete the drafting of the WLA policy document by the end of July 2019 and implement the framework in phases beginning with a six (6) month pilot in the first quarter of 2020.

The definition for WLA will also need to be reviewed and endorsed by WHO Expert Committees in the context of its usage in existing WHO guidelines in place of the term SRA. The WLA framework would also have implications regarding the abridged/streamlined procedures for prequalification of medicines/vaccines.

WHO invites interested and eligible regulatory authorities to volunteer for the pilot in order to gain experience with and help shape refinements to the proposed framework.

\textsuperscript{21} An NRArr is a regulatory authority that has reached Level 4 as established using the benchmarking tool and process established by PAHO/WHO in conjunction with the regulatory authorities of the Americas Region.

\textsuperscript{22} Based on experience, transparency is a proxy for a well-performing regulatory authority.
Given the wide interest in and implications associated with the definition and policy, WHO will adopt a multi-prong consultation process that includes:

- circulation of the draft policy including definitions through the routine WHO Expert Committee consultation processes, which includes posting for comment on the WHO website, circulation through the Expert Committee network and publication in WHO Drug Information;
- circulation through established Member State contact lists;
- presentation at relevant conferences and international/regional fora; and
- organization of dedicated consultative meetings (dates and location to be confirmed).

**ANNEX 1**

**Maturity level**

The WHO Global Benchmarking Tool (GBT) incorporates the concept of maturity levels, adapted from the International Standard ISO 9004:2009. This concept is not new within the context of regulatory systems benchmarking, having been implemented through the Benchmarking of the European Medicines Agencies (BEMA) since 2004. The concept has also been extensively discussed within WHO as well as during two WHO international consultations conducted in Geneva, Switzerland, in January and December 2015.

By applying the concept of maturity levels according to a well-defined algorithm, regulatory authorities are able to ascertain their level of development or ‘regulatory maturity’. The concept of maturity level also allows for the definition of more advanced systems that in turn should facilitate reliance and greater regulatory cooperation.

In applying the maturity level concept to the tool, the approach of defining critical indicators used in the earlier WHO vaccine tool has been eliminated.

Maturity of regulatory systems is divided into four levels: (1) some elements of regulatory systems exist; (2) evolving national regulatory system that partially performs essential regulatory functions; (3) stable well-functioning and integrated regulatory system; and (4) regulatory system operating at advanced level of performance and continuous improvement.

The attributes under each of the four levels are well defined, with full consideration of the WHO good regulatory practice principles.
Figure 2: Maturity levels

![WHO GBT Maturity Levels Diagram](image-url)

- **ISO 9004**
  - **1**: No formal approach
    - Some elements of regulatory system exist
    - Can ensure the quality of products if rely on ML3/ML4 regulatory systems
  - **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
    - Target of WHA Resolution 67.20
  - **4**: Continual improvement emphasized
    - Regulatory system operating at advanced level of performance and continuous improvement
    - Advanced and well resourced regulatory systems
ANNEX 2

Examples of WHO-Listed Authority designations

As noted, a regulatory authority may be designated a maturity level (ML) 3 or ML 4 WHO-Listed Authority (WLA) for the regulation of generic medicines, for new medicines and/or for vaccines, reflecting the current scope of the WHO benchmarking program.

A regulatory authority may also be designated a ML 4 WLA for one or more regulatory functions, such as inspection. In all cases, the listing would specify the scope of designation. To qualify for ML 4 listing for a specific regulatory function, the regulatory authority must at a minimum meet ML 3 WLA requirements for either medicine or vaccine regulation.

Examples of both types of listings are provided below, together with the scope of regulatory functions that would be assessed.

Example 1: Regulatory authority seeking ML 3 WLA recognition for generic medicines program

The National Regulatory System (RS) and following regulatory functions would be evaluated:

Registration and Marketing Authorization (MA), Vigilance (VL), Market Surveillance and Control (MC), Licensing Establishments (LI), Regulatory Inspection (RI), Laboratory Access and Testing (LA).

As the targeted product type/family is generic medicines, Clinical Trials Oversight (CT) and NRA Lot Release (LR) will be excluded from the evaluation. Note: Good Clinical Practice (GCP) inspection is covered under Regulatory Inspection (RI) in the GBT.

Example 2: Regulatory authority seeking ML 4 WLA recognition for good manufacturing practices (GMP) inspection function

Having attained ML 3 WLA status for generic medicines program, the same regulatory authority may subsequently decide to target ML 4 for a specific regulatory function, for example, GMP inspection. The GMP inspection function would then need to comply with relevant ML 4 indicators and be documented to consistently adhere to international standards before being designated ML 4.
ANNEX 3

Example of scoring and maturity level

Example of scoring results and maturity level by regulatory function for the evaluation of the regulation of medicines:

<table>
<thead>
<tr>
<th>NRA Function Assessed</th>
<th>Percentage Implemented</th>
<th>Maturity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-NATIONAL REGULATORY SYSTEM (RS)</td>
<td>81.0%</td>
<td>3</td>
</tr>
<tr>
<td>02-REGISTRATION AND MARKETING AUTHORIZATION (MA)</td>
<td>90.0%</td>
<td>3</td>
</tr>
<tr>
<td>03-VIGILANCE (VL)</td>
<td>85.0%</td>
<td>3</td>
</tr>
<tr>
<td>04-MARKET SURVEILLANCE AND CONTROL (MC)</td>
<td>85.0%</td>
<td>3</td>
</tr>
<tr>
<td>05-LICENSING ESTABLISHMENT (LI)</td>
<td>86.0%</td>
<td>3</td>
</tr>
<tr>
<td>06-REGULATORY INSPECTION (RI)</td>
<td>100.0%</td>
<td>4</td>
</tr>
<tr>
<td>07-LABORATORY TESTING (LT)</td>
<td>88.0%</td>
<td>3</td>
</tr>
<tr>
<td>08-CLINICAL TRIAL’S OVERSIGHT (CT)</td>
<td>90.0%</td>
<td>3</td>
</tr>
<tr>
<td>09-NRA LOT RELEASE (LR)</td>
<td>Not Applicable</td>
<td></td>
</tr>
</tbody>
</table>
QUALITY MANAGEMENT SYSTEM

REQUIREMENTS FOR NATIONAL INSPECTORATES

(July 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Valeria Gigante (gigantev@who.int), Technical Officer, Medicines Quality Assurance, with a copy to Ms Claire Vogel (vogelc@who.int) by 20 September 2019.

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.
QUALITY MANAGEMENT SYSTEM REQUIREMENTS FOR NATIONAL INSPECTORATES

BACKGROUND

During the Joint Meeting on Regulatory Guidance for Multisource Products (Copenhagen, July 2016), several World Health Organization (WHO) guidances were identified for update. In October 2016, the Fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) confirmed the need to update the selected guidances.

Following up on the recommendation from the Fiftieth ECSPP, the WHO Secretariat conducted a detailed analysis of the cluster of guidelines proposed for revision. The outcome of this analysis was discussed during the consultation on Good Practices for Health Products Manufacture and Inspection (Geneva, July 2018). In particular, considering that the WHO Quality System Requirements for National GMP Inspectorates (1) defines the basic requirements applicable to quality systems for the operation of inspection services within national regulatory authorities (NRA) concerned with GMP inspections, the WHO Secretariat proposed a strategy for revision that includes aligning the guidance with ISO 9001:2015 principles (2) and with Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) relevant guidance (3), as well as broadening its scope to include all GXP-related inspections conducted by a NRA.

The Fifty-second ECSPP endorsed the proposal for revision and recommended the WHO Secretariat to revise the WHO Quality System Requirements for National GMP Inspectorates aligning its content to international standards, the latest quality management systems (QMS) principles and to expanding the scope.
1. **INTRODUCTION**

1.1 This document describes the quality management system (QMS) requirements for the operation of inspection services within national regulatory authorities (NRA) or other state structures (for the purpose of this guidance, the term “NRA” will be used in the text to represent both NRA and other state structures). It is intended that each inspection service uses these requirements as the basis for developing and implementing its own QMS. Where the inspectorate operates under the umbrella of the NRA QMS, consideration should be given to the *WHO Guideline on the Implementation of Quality Management Systems for National Regulatory Authorities* (4).

1.2 The adoption of a common standard for QMS requirements is an essential element in achieving consistency in inspection practices and facilitating structured communication with other units of the NRA, as well as enabling mutual confidence and permitting recognition between pharmaceutical inspectorates.

2. **SCOPE**

This document outlines the QMS requirements for pharmaceutical inspectorates, competent for the oversight of GXP operations.

3. **GLOSSARY**

*corrective actions*
Steps taken to eliminate the cause of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again.

*good practices (GXP)*
Acronym for the group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacovigilance practices (GPP) and good distribution practices (GDP).

*internal audit*
An examination and assessment of all or part of a quality system with the specific purpose of improving it. An internal audit is usually conducted by an independent (of the function to be audited) and qualified team of experts designated by the management for this purpose.
quality indicators
Selected data intended to be monitored and used in assessing trends in performance.

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

quality manual
A document that includes the quality policy and objectives and describes the various elements of the QMS.

quality policy
A brief statement that describes the organization’s purpose, overall intentions and strategic direction, provides a framework for quality objectives and includes a commitment to meet applicable requirements.

rapid alert
An urgent notification submitted by a NRA participating in the Rapid Alert System concerning measures taken against a product placed on the market which poses a risk to consumers’ health and/or safety.

risk management
The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk.

standard operating procedure (SOP)
An authorized written procedure giving detailed instructions for performing a task or following a process in accordance with legislation, official guidance or internal standards.

4. QUALITY MANAGEMENT SYSTEM

4.1 QMS is a wide-ranging concept which covers all matters that are necessary to implement the inspectorate’s quality policy and to meet predefined objectives.

4.2 The QMS should define the inspectorate’s scope and context within the regulatory mandate as well as cover all functions, processes and activities
4.3 The primary aim of an inspectorate’s QMS is as follows:

a. to ensure its ability to consistently provide services that meet the organization’s objectives, as well as legal requirements and interested parties’ expectations; and

b. to facilitate continual improvement and provide a sound basis for sustainable development in compliance with statutory and regulatory requirements.

4.4 The QMS should at least describe and manage organizational structure, responsibilities, procedures, systems, processes and resources required, to provide value and achieve results for the inspectorate and relevant interested parties.

4.5 Typically, the legal basis for the establishment of the inspectorate, its mandate, the quality policy and the principles of the QMS should be documented in a quality manual or equivalent document.

4.6 The QMS should enable senior (“top”) management to best use available resources and systems in order to achieve the inspectorate’s targets and quality objectives. Senior management’s commitment and active participation is essential to ensure implementation of the QMS and to support of staff within the inspectorate.

5. CONTEXT OF THE INSPECTORATE

5.1 The legal basis for the establishment of the inspectorate, its mandate, as well as statutory and regulatory responsibilities and functions, should be clearly defined.

5.2 The inspectorate should determine its scope and its strategic direction in order to achieve the intended objectives.

5.3 The structure and operation of the inspectorate should be such that impartiality is safeguarded. Rules for deontology, confidentiality, ethics and conflict of interest should be clearly defined and obeyed. Where relevant, the inspectorate should implement a policy which distinguishes between the process of inspection and that of providing an advisory service. This service should be of benefit to all of industry and not solely to individual organizations.

5.4 The relationship of the inspectorate with other departments within the same NRA and other agencies and organizations outside the inspectorate, as well as any other stakeholders, should be described and documented where relevant.
MANAGEMENT AND LEADERSHIP

6.1 Senior management should make a formal commitment to the implementation of a documented quality policy that is compatible with statutory requirements and relevant objectives.

6.2 Senior management should ensure that inspectorate’s services and functions are aligned with regulatory requirements and NRA’s objectives, as well as meeting interested parties’ expectations.

6.3 Senior management is accountable for the integration of QMS requirements into the inspectorate’s processes and functions, for communicating the importance of QMS principles and for the overall effectiveness of the QMS. In addition, senior management should promote the application of risk management principles and support the engagement and contribution of personnel in improving the QMS.

6.4 Senior management should ensure that the pharmaceutical inspectorate has sufficient and appropriate resources at all levels to enable it to meet its objectives. Responsibilities, authorities and reporting structure for relevant roles should be clearly defined and documented in the QMS. The structure should be defined in organization charts.

6.5 An appropriately experienced and qualified person should be nominated as a QMS responsible person. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.

6.6 There shall be a system for periodic management review of the QMS effectiveness, including process improvements. Such reviews should be documented, and records should be maintained for a defined period.

7. MANAGEMENT SYSTEM PLANNING

7.1 The inspectorate should establish appropriate objectives for the intended level of service and of its functions that should be consistent with the quality policy and regulatory requirements. Risk management and sustainable development principles should be considered for the establishment of these objectives.

7.2 These objectives should be communicated to personnel at all levels and be updated whenever necessary.
7.3 Appropriate resources should be available to meet these objectives. Roles and responsibilities should be defined and, where appropriate, timelines for completion should be established. Systems for monitoring and evaluating results should be established. The inspectorate should maintain all necessary information on quality objectives.

7.4 The inspectorate should establish a documented change management system that should ensure that change requests are assessed, approved or rejected, that appropriate resources are allocated, and that roles and responsibilities are defined. Any change should be documented, communicated to the personnel and evaluated after implementation to ensure the objectives are met. The change management system should ensure that continual improvement is undertaken in a timely and effective manner.

8. **RESOURCES**

8.1 The inspectorate should have an organizational structure, required resources (financial, human, facilities and others) and documented procedures that enable it to meet its objectives, to perform inspection activities in accordance with official GXP guidelines and national legislation and carry out its functions and operations satisfactorily. Where necessary, measures and resources for the safety of personnel should be available.

**Personnel**

8.2 The inspectorate should employ the required personnel possessing the appropriate expertise to perform its functions, including inspections, and to determine whether the inspected entities comply with the principles of current GXP guidelines and with relevant legislation.

8.3 Personnel responsible for inspections should have appropriate qualifications, training, experience and knowledge of the inspection process and subject and should be periodically evaluated. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of good practices and the relevant legislation and be able to apply risk management principles in their decision-making process.
8.4 The inspectorate should ensure that induction and continuous training is provided to inspection personnel on administrative, regulatory and technical topics to maintain the inspectors’ competency aligned with current industry practice, technological advancements and regulatory changes. Training should be documented, and its effectiveness assessed periodically.

8.5 The inspectorate should maintain documented and up-to-date information on the relevant qualifications, training and experience of each inspector.

8.6 Personnel should have clear, up-to-date and documented job descriptions specifying their duties and responsibilities.

8.7 When products are procured from a third party and/or services are subcontracted to an external body or expert, the inspectorate should ensure that the third party meets predefined documented criteria, qualifications and the relevant requirements of the quality management system. Senior management should ensure that these external bodies or experts are periodically evaluated. Third party liability should be clearly defined in the contract or agreement.

8.8 All personnel employed or contracted by the inspectorate should obey the inspectorate’s code of conduct and should not be subject to any commercial, financial or other pressures which might affect their judgement and freedom to act. They should not be under the control of the pharmaceutical industry and must be assessed for potential conflict of interest. Personnel and third-party declarations of conflict of interest should be maintained, reviewed periodically and updated where necessary. It should be ensured that any decision-making process remains with the inspectorate and is not influenced by any third party.

**Infrastructure**

8.9 The inspectorate should provide personnel with the necessary infrastructure and appropriate work environment to support its functions and to enable meeting the quality objectives. Infrastructure includes, but is not limited to:

a. buildings, workspace, and associated facilities;
b. qualified equipment, including hardware and software;
c. transportation resources; and
d. information and communication technology.
9. DOCUMENTATION

9.1 The inspectorate should establish and maintain a system for the control of all documentation, including electronic files, relating to inspectorate’s QMS and activities. This should include policies, procedures, guidelines, records and any documents of external origin, such as legislation, which may directly or indirectly influence the activities of the inspectorate; or documents received from pharmaceutical companies and relevant organizations, as appropriate.

9.2 The inspectorate should ensure that its functions and operations are described in SOPs that clearly define the responsibilities, processes and actions. These may include, but not be limited to, training, inspections, reporting after inspections, handling of complaints, licensing (issue, suspension, withdrawal), certification, handling of quality, safety and efficacy issues, documentation control, change and deviation management, inspection planning, risk management and the handling of appeals.

9.3 The system and activities relating to advising on, issue, withdrawal, suspension of licenses, registrations, certifications and the application of other regulatory sanctions on facilities, organizations, products or operations, should be detailed in procedures and be in accordance with relevant guidelines and national legislation.

9.4 The inspectorate should establish procedures describing communication with other NRA units and external interested parties (e.g. industry, media) considering any statutory and regulatory requirements, where appropriate. Similarly, a procedure for exchanging regulatory information with other NRAs or national quality control laboratories should be available.

9.5 Activities relating to the sampling and testing of pharmaceutical products and raw materials should be described in a procedure which should also include the process for handling non-conforming products (e.g. substandard or falsified medical products).

9.6 The inspectorate should have procedures on handling quality, safety and efficacy issues which may lead to recall or the withdrawal of products from the market. Where applicable, the inspectorate should establish and maintain a system for communicating Rapid Alerts. Records of recalls and withdrawals should be maintained in accordance with national legislation.
9.7 The inspectorate should have documented procedures for dealing with complaints arising from its activities or those of its personnel and any contracted person or organization. A record should be maintained of all complaints received and the actions taken by the inspectorate. These records should be retained for a specified period of time.

9.8 The inspectorate should have procedures for consideration of appeals against its decisions.

9.9 The documentation control system should ensure that:

a. Documents are identified by title, author, reviewer, approver and unique identification. They should be dated and authorized by the appropriate persons prior to issue.

b. Current versions of documents are held by nominated personnel.

c. A register of all relevant documents and document holders should be maintained.

d. Superseded documents are withdrawn from use but are retained for defined periods of time.

e. Any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents.

f. Records relating to inspectorate’s activities and functions are readily available and are retained for an adequate period in line with legal requirements or internal standards.

g. Records comply with the relevant obligations under national legislation.

h. Records are safely stored during their retention period and held under conditions that guarantee their security and confidentiality unless otherwise required by national legislation. The destruction of records after their retention period follows a predefined procedure.

i. Electronic documentation and record management systems should provide at least the same level of assurance, compliance, accuracy and security as a manual system.
9.10 An inspection should be categorized in accordance with GXP guidelines (e.g. GMP, GDP, GCP) and its scope (e.g. product, process) and type (e.g. triggered, routine, follow-up) should be appropriately defined and documented.

9.11 The inspectorate should plan inspections in advance and elaborate a written programme as part of the inspectorate’s annual workplan. Risk management principles should be considered when establishing an inspection programme and prioritizing inspections as well as when conducting an inspection. Where repeated inspections of a company or organization have to be carried out, the frequency should be determined based on risk management principles defined in a procedure.

9.12 Inspection-related documents and records as defined in relevant inspection procedures (e.g. inspection plan, aide-memoire, checklists, worksheets and company documents and records) should be maintained for a defined period.

9.13 When more than one inspector is involved in an inspection, a lead inspector should be appointed to coordinate inspection activities. The inspection report should be prepared by the lead inspector with the assistance of all participating inspectors and/or experts and should be agreed upon by all participating inspectors and or experts.

9.14 The inspection report should follow a pre-approved format. Observations and/or data obtained in the course of inspection should be recorded in a timely manner in order to prevent loss of relevant information.

9.15 The inspection report should be sent to the inspected company or organization within the inspectorate’s established timelines. The lead inspector and all concerned inspectors and/or experts should participate in assessing the company’s response to determine the appropriateness of corrective and preventive actions as well as the GXP compliance status of the company or organization.

9.16 Completed inspections should be reviewed to ensure that requirements are met.
10. OPERATIONAL PLANNING AND PERFORMANCE EVALUATION

10.1 An annual workplan should be developed, documented and periodically reviewed by senior management, including all inspectorate’s activities in accordance with a written procedure. Regulatory, statutory and scientific requirements should be taken into account during the planning of operations and services. Consideration should also be given to the availability of required resources and the ability to consistently provide services that meet legislative requirements and stakeholder expectations. Risk management principles should be used during planning to determine, monitor and manage risks and to identify opportunities for process improvements. Any changes to the workplan should follow the inspectorate’s change management system.

10.2 Appropriate quality indicators and methods should be established in order to monitor and periodically evaluate the inspectorate’s processes and level of improvement and service (including contracted-out services) and demonstrate that they were carried out as planned and met predefined quality objectives. These quality indicators, methods, analyses and results should be documented.

10.3 The results of the analyses should be used to evaluate the performance and effectiveness of the QMS, the adequacy of actions taken to address risks and the need for further improvements.

Internal Audits

10.4 The inspectorate should implement a system of periodic and documented internal audits of its operations to assess compliance with the requirements of the QMS. Internal audits should be conducted at least once a year.

10.5 Internal audit processes, criteria, scope and documents should be defined. Auditors qualifications and selection criteria should be documented. Internal audit records, including the findings, conclusions, recommendations and follow-up actions, should be retained for a defined period.

10.6 Corrective actions corresponding to audit findings should be identified, documented and implemented in a timely manner. The effectiveness of these actions should be evaluated, and the risk plan should be updated to take note of the root causes to the non-conformances.
Management Review

10.7 Senior management should review the inspectorate’s QMS at planned intervals to ensure its continuing suitability, adequacy, effectiveness and alignment with the inspectorate’s strategic direction and legislative requirements. Management reviews should be conducted at least once a year.

10.8 A management review should include, but not be limited to:
   a. the status of the actions from previous management reviews;
   b. any internal or external changes affecting the QMS;
   c. any deviations affecting the functionality of the QMS;
   d. the extent to which quality objectives have been met;
   e. process performance analyses;
   f. audit results and effectiveness of corrective actions;
   g. complaints and appeals;
   h. adequacy of resources;
   i. any identified risks and mitigation measures; and
   j. opportunities for improvements.

11. PUBLICATIONS

11.1 The inspectorate should issue and maintain an up-to-date list of inspected and licensed facilities and organizations, including information on the outcome of inspections. This list may become publicly available in accordance with national legislation.

11.2 The inspectorate should ensure that other relevant publications, such as technical guides, GXP guidelines and regulatory requirements, are publicly available.

References


Further reading


***
PROCEDURE FOR THE ELABORATION, REVISION AND OMISSION
OF MONOGRAPHS AND OTHER TEXTS FOR
THE INTERNATIONAL PHARMACOPOEIA

Draft revision for The International Pharmacopoeia

(June 2019)

DRAFT FOR COMMENTS

Please send any comments you may have on the attached text to Dr Herbert Schmidt, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (schmidt@who.int) by 20 August 2019.

Medicines Quality Assurance working documents will only be sent out electronically and will also be placed on the Medicines website for comment under “Current projects”.

If you have not already received our draft working documents, please send your email address to jonessi@who.int and we will add your name to our electronic mailing list.

[Note from the Secretariat. The International Pharmacopoeia constantly develops new monographs and other texts and revises existing ones to stay abreast of advances in analytical science and regulatory matters. The following text describes the life cycle of compendial texts: how they are developed, revised and, if appropriate, finally omitted from the compendium. The text also covers steps related to the establishment of the International Chemical Reference Substances referred to in analytical tests.]
Procedure for the elaboration, revision and omission of monographs and other texts for The International Pharmacopoeia

Introduction

Monographs in The International Pharmacopoeia are essential standards to ensure the quality of medicines, thus contributing to their safe and efficacious use. They are developed and maintained in an open and transparent process, in line with the principles outlined in the Good Pharmacopoeial Practices (GPhP)\(^\text{23}\) and aimed to foster harmonization and convergence of compendial quality standards to ultimately increase access to affordable, quality-assured medicines.

The following procedure describes the life cycle of texts in The International Pharmacopoeia: how they are developed, revised and, if appropriate, finally omitted from the compendium. The text also covers steps related to the establishment of the International Chemical Reference Substances (ICRS) referred to in analytical tests.

Elaboration of monographs\(^\text{24}\)

The steps of the development procedure are as follows\(^\text{25,26}\):

Step 1: Identify medicines for which pharmacopoeial monographs need to be developed or revised. Set up a biannual work plan prioritizing medicines that are included in the WHO Model List of Essential Medicines (or are otherwise relevant for WHO health programmes), preferably not already described in pharmacopoeias. Determine whether or not monographs for the corresponding active pharmaceutical ingredients also need to be developed or revised. Confirm the work plan with all WHO parties concerned, including the Department of Essential Medicines and Health Products, specific disease programmes and the Prequalification Team – Medicines.

Step 2: Share the work plan with other pharmacopoeias and identify ways of collaboration to reduce the workload of the monograph development and to promote converged or harmonized quality standards that are globally applicable and recognized.

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\(^{24}\) It is intended to add a section on the revision of monographs at a later stage.

\(^{25}\) The procedure for the elaboration, revision and omission of monographs and other texts for The International Pharmacopoeia was developed by the Secretariat of The International Pharmacopoeia in consultation with the partners involved: Expert, WHO Collaborating Centre, collaborating laboratories and the WHO custodian organization for the establishment, storage and distribution of ICRS, the European Directorate for the Quality of Medicines & HealthCare. The steps are therefore described from the perspective of all partners involved.

\(^{26}\) The steps are listed in their chronological order. However, certain steps may overlap during the development of monographs and other compendial texts.
Step 3: Contact manufacturers of WHO prequalified medicines and/or of medicines authorized by WHO listed national regulatory systems with an appropriate maturity level\(^{27}\) to request quality control (QC) specifications and samples of their products.

Step 4: Search for relevant information on the product in the public domain, including other pharmacopoeias.

Step 5: Assign WHO Collaborating Centres, collaborating laboratories and/or specific experts, if appropriate, to participate in the establishment or revision of the monograph.

Step 6: Set up a first version of the monograph based on the available information and on discussions with the partners involved. Perform laboratory investigations to develop, adapt, optimize, verify or validate the proposed analytical procedures. Verify the suitability of the proposed specifications by analyzing medicines from different regions or markets of the world. Identify which of the required reference substances would need to be newly established or are already available either as ICRS or as reference substances established by another pharmacopoeia. In case reference is made to already established ICRS or reference substances established by other pharmacopoeia include these reference substances in the laboratory investigations and advise on their suitability for the new intended use(s). Issue a laboratory report describing the tests performed and the results obtained. Based on mutual agreements, share the laboratory report with other pharmacopoeias with a view to foster harmonization and convergence of compendial quality standards.

Step 7: Follow the consultative process of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP). Circulate the draft text for comments and provide the document on the website of The International Pharmacopoeia.

Step 8: Collate the comments received during the public consultation and review them with the partners involved. If necessary, arrange with the laboratories involved additional laboratory investigations.

Step 9: Discuss the comments received and, if applicable, the results of the additional investigations at an informal consultation with experts. Revise the draft text based on the discussions, as appropriate.

Step 10: Repeat steps 7 to 10 until the text is deemed suitable for adoption.

\(^{27}\) It is intended to refer in the final version of the document to the WHO Global Benchmarking Tool, which is currently under discussion.
Step 11: Identify and contact manufacturers (or other potential donors of candidate materials) to ascertain the availability of candidate materials for the establishment of the ICRSs described in the text. Discuss with the WHO custodian organization for the establishment, storage and distribution of ICRS, the European Directorate for the Quality of Medicines & HealthCare (EDQM), the strategy to establish the proposed ICRSs and its impact on the analytical provisions of the monograph.

Step 12: Submit the draft monograph (together with the laboratory report and a compilation of the comments received during the public consultation) to the ECSPP for information, discussion and/or possible adoption, depending on the maturity of the monograph. If the text is adopted, proceed with step 13. If not, repeat steps 7 to 11.

Step 13: Incorporate all changes agreed during the final discussions leading to adoption, together with any editorial changes.

Step 14: Confirm the final text with the experts and laboratories involved in the final discussions and publish the adopted monograph in a new edition or supplement of The International Pharmacopoeia.28

Step 15: Identify already established ICRS referred to in the monograph. Review the ICRS establishment report(s) to evaluate if the intended uses and the quantity per vial are still valid and appropriate or need to be amended or revised in view of the analytical provisions of the new standard.

Step 16: Identify newly to be established ICRS referred to in the monograph. Revert to potential donors of candidate material (Step 11) and initiate the shipment of the material to the WHO custodian organization in charge of ICRSs.

Step 17: Perform laboratory investigations to characterize the candidate material and/or to ensure the suitability of the material for its new or revised intended uses. Issue an ICRS establishment or re-establishment report. If information in the ICRS leaflet of already established ICRS has to be revised, assign a new batch number to the ICRS.

Step 18 Submit the establishment report to the ICRS Board. Start the distribution of the ICRS after the reference substance is released by the ICRS Board and the corresponding new monograph is published.

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28 Subject to the availability of the necessary resources, the Secretariat aims to publish adopted texts for inclusion in The International Pharmacopoeia after each meeting of the ECSPP.
Step 19: Submit the ICRS report to the ECSPP to confirm the release of the reference standard and/or the change(s) in the leaflets.

**Omission of monographs**

Step 1: Identify monographs on medicines (or other pharmaceutical products) that are described in *The International Pharmacopoeia* but are no longer included in the WHO Model List of Essential Medicines or otherwise relevant for WHO health programmes.

Step 2: Submit the list of monographs (and other texts) proposed for omission to the ECSPP for possible approval.

Step 3: Transfer omitted texts to a publicly accessible archive section on the WHO website, together with the following note: “These monographs will neither be updated or revised, nor will the corresponding International Chemical Reference Substances be further monitored. Users will need to ensure that the product complies with current rules and regulations governing medicines and related products in their respective territories.”

Step 4: Remove the ICRS referred to in omitted monographs from the ICRS catalogue one year after the monograph has been transferred to the archive page on the WHO website.

**Elaboration, revision and omission of other pharmacopoeial texts**

In principle, the steps outlined above apply to all texts. Some specific texts may, however, necessitate deviations. The steps in the development of pharmacopoeial texts, however, shall always include public consultation, consideration of comments received, if appropriate, and adoption of the texts by the ECSPP.
GOOD CHROMATOGRAPHY PRACTICES

(July 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 20 September 2019.

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.
GOOD CHROMATOGRAPHY PRACTICES

1. INTRODUCTION AND SCOPE

The use of chromatography methods such as High-Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) in quality control laboratory analysis has increased significantly in recent years. Observations during inspections have shown that there was a need for a specific good practices document.

HPLC and GC methods are used, for example, the identification of materials and products, for determination of assay and related substances in materials and products, as well as in validation such as process validation and cleaning validation. (Note: Although Thin-Layer Chromatography (TLC) methods are also used, this approach is not specifically addressed in this document.)

Due to the criticality of the results obtained through chromatography, it must be ensured that the data acquired meet ALCOA+ principles (i.e. attributable, legible, contemporaneous, original and accurate).

This document provides information on good practices to be considered in the analysis of samples when chromatographic methods and systems are used. The principles should be applied in the analysis of, for example, raw materials, starting materials, intermediates, in-process materials and finished products.

The principles contained in this guideline are applicable to all types of chromatographic analysis used in, for example, assay determination, testing for related substances and impurities, process validation, cleaning validation, cleaning verification and stability testing.

2. GLOSSARY

**ALCOA**
A commonly used acronym for “attributable, legible, contemporaneous, original and accurate”.

**ALCOA+**
A commonly used acronym for “attributable, legible, contemporaneous, original and accurate” which puts additional emphasis on the attributes of being complete, consistent, enduring and available – implicit basic ALCOA principles.
**audit trail**
The audit trail is a form of metadata that contains information associated with actions that relate to the creation, modification or deletion of good practices (GXP) records. An audit trail provides for secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the “who, what, when and why” of the action.

**Backup**
A backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (for example, in the event of a system crash or corruption of a disk). It is important to note that backup differs from archival in that backup copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically overwritten. Such temporary backup copies should not be relied upon as an archival mechanism.

**Calibration**
The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

**Chromatographic column**
A tube commonly filled with a stationary phase over which a sample and mobile phase move, used in chromatographic analysis.

**Data**
All original records and true copies of original records, including source data and metadata and all subsequent transformations and reports of these data, which are generated or recorded at the time of the good manufacturing practices (GMP) activity and allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio- or video-files, or any other media whereby information related to GMP activities is recorded.
Data integrity
Data integrity is the degree to which data are complete, consistent, accurate, trustworthy and reliable and that these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

Exponential curve fitting
The drawing of a curve using an exponential equation through the start and end of the child peak. The curve passes under each child peak that follows the parent peak; the area under the skim curve is subtracted from the child peaks and added to the parent peak.

Exponential skim
The creation of a curvature in the skim line in an attempt to approximate the underlying baseline of the parent peak.

Front peak skim
The process of integrating child peaks on the front (upslope) of a peak subject to specified criteria.

Integration
The process of applying specified parameters for chromatographic peaks (determination of height, area and retention time).

Metadata
Metadata is data about data that provides the contextual information required to understand those data. These include structural and descriptive metadata. Such data describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in weighing, the number 8 is meaningless without metadata, such as, the unit, milligram, etc. Other examples of metadata include the time/date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

Peak valley ratio
The peak to valley ratio is a measure of quality indicating how well the peak is separated from other substance peaks.
**Qualification**
Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications properly installed, and/or work correctly, and lead to the expected results.

**Rear peak skim**
The process of integrating child peaks on the tail (downslope) of a peak subject to specified criteria.

**Restoration**
The process of retrieving electronic data that had previously been backed-up and presented in a readable format.

**Source data**
Original data obtained as the first-capture of information, whether recorded on paper or electronically.

**Straight line skim**
The process of drawing a straight line through the start and end of a child peak. The height of the start of the child peak is corrected for the parent peak slope. The area under the straight line is subtracted from the child peak and added to the parent peak.

**Tangential skim**
The process of integrating a small peak located on the tailing edge of a larger peak. The baseline of the small peak becomes a tangent drawn from the valley of the larger peak to the tangent point on the chromatogram.

**Validation**
Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

**Valley height ratio**
Valley height ratio is the ratio of the height of the child peak above the baseline to the height of the valley above the baseline. This ratio must be smaller than the specified value for the child peak to be skimmed.
3. **CHROMATOGRAPHIC SYSTEMS**

3.1. Chromatographic systems should meet regulatory requirements and expectations for GXP. This should include, for example, ensuring that data are acquired, processed and stored in accordance with national legislation and ALCOA+ principles.

3.2. Vendor qualification should ensure that hardware and software are suitable for their intended application.

3.3. Valid agreements should specify the respective responsibilities between the purchaser and supplier and include arrangements for after-sales services.

3.4. Chromatographic systems selected and installed, should be appropriate for their intended use.

4. **QUALIFICATION, VALIDATION, MAINTENANCE AND CALIBRATION**

4.1. The scope and the extent of validation and qualification of chromatographic systems should be determined based on risk management principles. This includes hardware and software.

4.2. The approach to, and execution of validation and qualification, should be described in an authorized document such as a validation master plan.

4.3. All stages of qualification should be considered and may include, for example, user requirement specifications (URS), design qualification (DQ), factory acceptance test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). (See also the *WHO GMP: Guidelines on validation, Appendix 5: validation of computerized systems and Appendix 6: Guidelines on qualification*, Annex 3, TRS 1019, 2019).

4.4. Validation and qualification should be described in protocols and recorded in reports. Reports should contain documented evidence and include, for example, screen shots, printouts or other source data and metadata of tests executed as part of validation and qualification.

4.5. The data should provide evidence of the consistency of performance of the system and reliable and accurate results.
4.6. Parameters such as, but not limited to, password control, audit trail, access and privileges should be described and verified during validation and qualification.

4.7. Maintenance, preventive maintenance and calibration of chromatographic systems should be done in accordance with written procedures. Records should be maintained.

4.8. Root cause analysis, impact assessment and risk assessment should be done when any calibration parameter is found out of calibration or not meeting the predefined limits. Appropriate corrective and preventive action (CAPA) should be taken and documented.

5. **ACCESS AND PRIVILEGES**

5.1. There should be a standard operating procedure (SOP) for the creation and deletion of user groups and users of the chromatographic system indicating the relevant privileges allocated to each user. Records should be maintained.

5.2. An up-to-date record of user groups and users should be maintained.

5.3. Users in each group should be appropriately qualified for the responsibility and privileges allocated.

5.4. Where required, justification should be provided for privileges granted to user groups or users.

5.5. Manual records of user groups, users and their privileges should be concordant with electronic data.

6. **AUDIT TRAIL**

6.1. Chromatographic systems should have an audit trail(s) which reflects, for example, users, dates, times, original data and results, changes and reasons for change. (See also *WHO Guidance on good data and record management practices, TRS 996, Annex 5, 2016*.)

6.2. Full audit trails should be enabled from the time of installation of software.

6.3. Audit trails should remain enabled throughout the life cycle of a chromatographic system.
6.4. Audit trails should be reviewed in accordance with an SOP. There should be evidence of the regular review of an audit trail (for example, each sample sequence or sample set in chromatographic analysis) and of the periodic review of audit trails. (Periodic review should be done at specified intervals where a random selection of audit trails are verified and may include system audit trail, changes in user privileges and other activities tracked in audit trails).

6.5. Audit trails are part of metadata and should be stored as part of the data set for all chromatographic analysis.

7. **DATE AND TIME FUNCTIONS**

7.1. Chromatographic systems should have date and time functions enabled from the time of installation of the software.

7.2. The date and time function should be locked and access to change the date and time should be controlled. (This includes changes to time zone setting.)

7.3. All actions on chromatographic systems should be date- and time-tracked.

8. **ELECTRONIC SYSTEMS**

(Note: This includes computerized systems.)

8.1. Written procedures should be followed when a new electronic system is taken into use. Procedures should also be followed for the removal of a system from use. Records should be maintained.

8.2. Software selected, installed and applied for acquisition, processing and calculation of results, should be suitable for their intended use; validated and render results meeting regulatory, GXP and ALCOA+ principles.

8.3. It is preferable that all chromatographic systems be linked to a network system where data is stored and managed on a centralized server.

8.4. Stand-alone systems should be appropriately managed. Risk assessment should be done to ensure that sufficient controls are in place to eliminate the risks associated with stand-alone systems. These include, but are not limited to, access, privileges, date and time function, audit trail, data back-up and data management.
8.5. Electronic Data Management Systems (EDMS) should be considered for the appropriate management of data, including acquisition, processing and storage of data. EDMS should be appropriate for their intended use and ensure the accuracy and reliability of data acquired and processed.

9. SOLVENTS, BUFFER SOLUTIONS AND MOBILE PHASES

9.1. Solvents, buffer solutions and mobile phases should be prepared, stored and used in accordance with authorized specifications, procedures and pharmacopoeia. These should be used within appropriate, scientifically justifiable timelines.

9.2. Records for their preparation and use should be maintained.

9.3. Chemicals, reagents and other materials used should be of appropriate grade and quality.

9.4. Mobile phases should be filtered and degassed as required.

10. COLUMN MANAGEMENT

10.1. Columns used in chromatography should be appropriate for their intended use.

10.2. Columns should be purchased from approved suppliers.

10.3. Columns should be verified on receipt and checked for their suitability prior to use.

10.4. Tubing and fittings should be appropriate to ensure that the system performs as expected.

10.5. Column efficiency (number of theoretical plates) should be assured to ensure good chromatography.

10.6. Equilibration of columns, as well as controlling temperature and mobile phase during analysis, should be done when specified.

10.7. The required flow rate should be specified in relevant test procedures; and should be appropriate for the column to be used to ensure optimal chromatographic separation without exceeding recommended maximum backpressure.

10.8. The use of columns should be recorded in a traceable manner. This includes, for example, the unique column identification number, number of injections and washing of the column.
10.9. Columns should be washed (cleaned or flushed) according to defined procedures describing the steps and parameters, such as sequence, flow rate and time.

10.10. Columns should be stored in a manner that ensures that they are not damaged.

10.11. Removal of contaminants and regeneration of columns should only be considered when the appropriate procedures for this have been developed.

11. SAMPLE MANAGEMENT

11.1. Sample management (including the receiving and preparation of samples) should be considered an important aspect in good chromatography practices.

11.2. Samples received for analysis should be entered in an appropriate record which ensures the traceability of the sample detail and analysis.

11.3. Samples should be stored under appropriate conditions.

11.4. Samples (as well as blank and standard solutions) should be prepared in accordance with the authorized specifications and standard test procedures. Records for the preparation should be maintained.

11.5. Official, secondary or working standards used should be traceable to the records maintained for their purchase, preparation and storage.

11.6. Standard and sample solutions prepared for use in chromatography should be used within defined time lines derived from analytical procedure validation and stability data as appropriate.

11.7. Validated or verified (as applicable) analytical methods should be used.

11.8. The sample set (sample sequence) should be defined. The vials with standard solution(s), sample solution(s) and blank solution(s) should be verified to ensure the correct sequence of injections in the chromatographic system before starting the sequence of injections.

11.9. Where carry-over or interference in analysis is relevant, suitable precautions should be taken.
11.10. The use of “trial injections”, “system check injections” or other injections that are not specified as part of a sample set, is not recommended. In exceptional cases where this is done, authorized procedures should clearly describe this approach and specify that only standard solutions may be used for this purpose. The electronic record of results in such cases should be saved and stored together with the results of the sample set for analysis.

11.11. A System Suitability Test (SST) should be part of the sample set. The SST should be performed as described in the respective pharmacopoeia monograph or validated in-house specification and standard test procedure. The SST should meet the pre-defined acceptance criteria.

11.12. Acceptance criteria should be set for SST, bracketing standards, deviation from relative retention and any other aspect that may be deemed necessary for the chromatographic analysis. This includes acceptability of peak shapes.

11.13. Bracketing standards (standard solution injections) should be included in the sample set, at defined intervals, where appropriate. The number of bracketing standards included in a sample set should be defined. Compliance with the defined acceptance criteria should be verified.

11.14. Where blank interferences are detected, these should be within limits.

12. CHROMATOGRAPHIC METHODS (ACQUISITION AND PROCESSING)

12.1. Chromatographic methods should be suitable for their intended use. Appropriate values should be specified for parameters such as, slope sensitivity, noise threshold, peak width, area threshold, bunching factor and skim ratio.

12.2. Where non-pharmacopoeia methods are to be used, these should be developed, validated and described in detail in standard procedures. These procedures should be followed by qualified, trained, experienced personnel.

12.3. It is preferable that methods are created and saved in the chromatographic system by authorized personnel. The method selected for analysis from the saved methods should not be modified unless approved for the intended purpose by authorized personnel.

12.4. Results acquired should be processed by validated methods. Methods for acquisition and processing selected should be traceable and reflected in the audit trail.

12.5. Methods should be proven to remain in a validated state throughout their life cycle.
13. CHROMATOGRAPHIC PEAKS

13.1. Chromatographic analysis should be done in accordance with procedures which include the recommendations and considerations for good chromatography practices as described in this guideline with specific reference to policies, acceptance limits (as appropriate) and ALCOA+.

13.2. In addition to parameters such as accuracy, precision and linearity (see WHO Guideline on Validation of Analytical Methods), the following factors should also be considered during analytical method validation and appropriately applied during sample analysis:

- slope sensitivity;
- peak width;
- bunching factor;
- noise threshold; and
- area threshold.

13.3. Where more than one column has to be used in complex analysis, the procedure and instructions should be clear in order to ensure that no errors are made during analysis.

13.4. Peaks should be reviewed for acceptability according to policies and procedures, including recommendations and requirements from national regulatory authorities, pharmacopoeia and analytical validation.

14. PEAK INTEGRATION

14.1. Peak areas in chromatograms should be accurately and consistently integrated in a scientifically sound manner.

14.2. Where possible, HPLC and GC instruments should be interfaced with computerised chromatographic data capturing and processing systems which are capable of applying integration parameters set, automatically and consistently.

14.3. The same integration parameters should be applied to all peaks in a sample set or sample sequence unless otherwise scientifically justifiable.
14.4. To facilitate the accurate integration of chromatographic peaks, it is necessary that all of the peaks are fully separated. If quantitative data must be obtained from unseparated peaks, the laboratory should have clear policies as to how such peaks should be integrated. This should include a description as to when it is acceptable to use different functions for integrating unresolved peaks, such as:

- tangential skim;
- exponential skim;
- exponential curve fitting;
- straight line skim;
- front peak skim;
- rear peak skim;
- peak valley ratio; and
- valley height ratio.

14.5. Validated methods, specified chromatographic conditions and good chromatography practices should facilitate obtaining symmetrical peaks. Where fronting, tailing, split peaks or other types of peaks are observed, these should be investigated, the root cause identified and appropriate CAPA taken.

14.6. Where manual integration has to be done, authorized procedures should be followed. Records should be maintained which include the authorization and justification for manual integration.

14.7. Using a procedure to integrate peak height or area by manually setting the baseline using chromatographic software should only be allowed in exceptional cases. Only trained, experienced users should be granted privileges to do so. Records and justification should be given when this procedure is followed.

14.8. Where smoothing is applied, the type of “filter” used and extent of smoothing should be justified.
15. CLEANING VALIDATION

(Note: For recommendations relating to cleaning validation, see Annex 4, Supplementary Guidelines on Good Manufacturing Practices: Validation (WHO Technical Report Series, No. 937, 2006, Appendix 3.)

15.1. Where possible, specific methods (such as in chromatography) should be developed, validated and then used in cleaning validation and cleaning verification.

15.2. Chromatographic methods selected should be specific and appropriate to detect the presence of the substance to be analysed.

15.3. Data (results and metadata) should be managed in accordance with these guidelines and other relevant guidelines relating to cleaning validation, chromatography, data integrity and applicable chapters in pharmacopoeia.

15.4. Data and results should be retained for appropriate times to enable inspection thereof.

16. DATA MANAGEMENT

16.1. Chromatographic data should be managed in accordance with this guideline and other related guidelines such as Good Data and Record Management.

16.2. Procedures should be followed for the processing of data and reporting of results.

16.3. Data should be backed up according to procedures and records maintained as proof thereof. Special care should be taken to ensure frequent back up of data from stand-alone systems to prevent loss of data.

16.4. Data should be safely stored, including control over access to data. Backed-up data should be randomly selected for restoration and verification, at defined intervals.

16.5. Where appropriate, hard copies of data (including metadata) and results should be retained as part of the analytical report reflecting analysis performed.

(Note: See other guidelines addressing computerized systems, data integrity and good documentation practices.)

16.6. Procedures should be in place to allow for recovery of chromatographic data in case of disasters such as instrument failure, viruses, hardware or software failure and power failure.
16.7. Complete data should be retained for appropriate periods of time to allow for data verification, registration or other reasons.

**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
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<tr>
<td>CAPA</td>
<td>corrective and preventive action</td>
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<tr>
<td>DQ</td>
<td>design qualification</td>
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<tr>
<td>EDMS</td>
<td>Electronic Data Management Systems</td>
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<td>FAT</td>
<td>factory acceptance test</td>
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<td>GC</td>
<td>gas chromatography</td>
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<td>GMP</td>
<td>good manufacturing practices</td>
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<td>GXP</td>
<td>good practices</td>
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<td>HPLC</td>
<td>High Pressure Liquid Chromatography</td>
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<tr>
<td>ID</td>
<td>operator identification</td>
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<tr>
<td>IQ</td>
<td>installation qualification</td>
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<td>OQ</td>
<td>operational qualification</td>
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<td>PQ</td>
<td>performance qualification</td>
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<td>SAT</td>
<td>site acceptance test</td>
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<td>SOP</td>
<td>standard operating procedure</td>
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<td>SST</td>
<td>system suitability</td>
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<td>TLC</td>
<td>Thin Layer Chromatography</td>
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<td>URS</td>
<td>user requirement specifications</td>
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**Further reading**


GOOD STORAGE AND DISTRIBUTION PRACTICES
FOR MEDICAL PRODUCTS
(August 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by 20 September 2019.

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 email address to jonessi@who.int and your name will be added to our electronic mailing list.
GOOD STORAGE AND DISTRIBUTION PRACTICES FOR MEDICAL PRODUCTS

1. INTRODUCTION

1.1 Storage and distribution are important activities in the supply chain management of medical products. Various people and entities may be responsible for the handling, storage and distribution of medical products. Medical products may be subjected to various risks at different stages in the supply chain, for example, purchasing, storage, repackaging, relabelling, transportation and distribution.

1.2 Substandard and falsified products are a significant threat to public health and safety. Consequently, it is essential to protect the supply chain against the penetration of such products.

1.3 This document sets out steps to assist in fulfilling the responsibilities involved in the different stages within the supply chain and to avoid the introduction of substandard and falsified products into the market. The relevant sections should be considered as particular roles that entities play in the storage and distribution of medical products.

1.4 This guideline is intended to be applicable to all entities involved in any aspect of the storage and distribution of medical products, from the premises of the manufacturer of the medical product to his or her agent, or the person dispensing or providing medical products directly to a patient. This includes all entities involved in different stages of the supply chain of medical products, manufacturers and wholesalers as well as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents and their employees.

1.5 The relevant sections of this guideline should also be considered for implementation by, amongst others, governments, regulatory bodies, international procurement organizations, donor agencies and certifying bodies, as well as all health care workers.

1.6 This guideline can be used as a tool in the prevention of the distribution of substandard and falsified products. It should however be noted that these are general guidelines which may be adapted to suit the prevailing situations and conditions in individual countries. National or regional guidelines may be developed to meet specific needs and situations in a particular region or country.
1.7 To maintain the quality of medical products, every party active in the supply chain has to comply with the applicable legislation and regulations. Every activity in the storage and distribution of medical products should be carried out according to the principles of good manufacturing practices (GMP) (1), good storage practices (GSP) (2) and good distribution practices (GDP) (3), as applicable.

1.8 This guideline does not deal with dispensing to patients as this is addressed in the World Health Organization (WHO) Good Pharmacy Practice (GPP) (4).

1.9 This guideline should also be read in conjunction with other WHO guidelines.

2. SCOPE

2.1 This document lays down guidelines for the storage and distribution of medical products. It is closely linked to other existing guidelines recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, such as referenced below.

2.2 Depending on the national and regional legislation, these guidelines may apply equally to medical products for human and veterinary use.

2.3 The document does not specifically cover GMP aspects of finished products in bulk, distribution of labels or packaging as these aspects are considered to be covered by other guidelines. The principles for the distribution of starting materials (active pharmaceutical ingredients (APIs) and excipients) are also not covered here. These are laid down in the WHO document Good Trade and Distribution Practices for Pharmaceutical Starting Materials (5).

3. GLOSSARY

The definitions provided below apply to the words and phrases used in this guideline. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents.

**active pharmaceutical ingredient (API).**
Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used in the production of a drug, becomes an active ingredient of that drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.
**ALCOA.**
A commonly used acronym for “attributable, legible, contemporaneous, original and accurate”.

**auditing.**
An independent and objective activity designed to add value and improve an organization’s operations by helping the organization to accomplish its objectives by using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

**batch.**
A defined quantity of pharmaceutical products processed in a single process or series of processes so that it is expected to be homogeneous.

**batch number.**
A distinctive combination of numbers and/or letters which uniquely identifies a batch, for example, on the labels, its batch records and corresponding certificates of analysis.

**broker.**
Arranges transactions in relation to the sale or purchase of medical products that consist of negotiating, independently and on behalf of another legal or natural person, and that do not include physical handling.

**consignment.**
The quantity of pharmaceutical products supplied at one time in response to a particular request or order. A consignment may comprise of one or more packages or containers and may include pharmaceutical products belonging to more than one batch.

**container.**
The material employed in the packaging of a pharmaceutical product. Containers include primary, secondary and transportation containers. Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.

**contamination.**
The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material, intermediate or pharmaceutical product during handling, production, sampling, packaging or repackaging, storage or transportation.

**contract.**
Business agreement for the supply of goods or performance of work at a specified price.
corrective and preventative actions (CAPA).
A system for implementing corrective and preventive actions resulting from an investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings and trends from process performance and product quality monitoring.

cross-contamination.
Contamination of a starting material, intermediate product or finished pharmaceutical product with another starting material or product during production, storage and transportation.

distribution.
The procuring, purchasing, holding, storing, selling, supplying, importing, exporting or movement of pharmaceutical products, with the exception of the dispensing or providing pharmaceutical products directly to a patient or his or her agent.

excipient.
A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system to aid in the processing of the drug delivery system during its manufacture; protect, support or enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

expiry date.
The date given on the individual container (usually on the label) of a pharmaceutical product up to and including the date on which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf life to the date of manufacture.

falsified product.
A product that has been deliberately and/or fraudulently misrepresented as to its identity, composition or source. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized product or the manufacture of a product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized product. “Composition” shall refer to any ingredient or component of the product in accordance with applicable specifications authorized/ recognized by the NRA. “Source” shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable. (Reference Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products. Report by the Director-General; 2017, http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf )
**First Expiry/First Out (FEFO).**
A distribution procedure that ensures that the stock with the earliest expiry date is distributed and/or used before an identical stock item with a later expiry date is distributed and/or used.

**Forwarding Agent.**
A person or entity engaged in providing, either directly or indirectly, any service concerned with clearing and forwarding operations in any manner to any other person and includes a consignment agent.

**Good Distribution Practices (GDP).**
That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities which occur during the distribution process, as well as providing a tool to secure the distribution system from falsified, unapproved, illegally imported, stolen, substandard, adulterated and/or misbranded pharmaceutical products.

**Good Manufacturing Practices (GMP).**
That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

**Good Pharmacy Practice (GPP).**
The practice of pharmacy aimed at providing and promoting the best use of medicines and other health care services and products by patients and members of the public. It requires that the welfare of the patient is the pharmacist’s prime concern at all times.

**Good Practices (GXP).**
Acronym for the group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacovigilance practices (GPP) and good distribution practices (GDP).

**Good Storage Practices (GSP).**
That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage thereof.

**Good Trade and Distribution Practices (GTDP).**
That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the numerous activities which occur during the trade and the distribution process.
heating, ventilation and air conditioning systems (HVAC).
Heating, ventilation and air-conditioning, also referred to as environmental control system (ECS).

importation.
The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

intermediate product.
Partly processed product that must undergo further manufacturing steps before it becomes a bulk finished product.

labelling.
Process of identifying a pharmaceutical product including the following information, as appropriate: name of the product; active ingredient(s), type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; names and addresses of the manufacturer and/or the supplier.

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

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

material.
A general term used to denote starting materials (APIs and excipients), reagents, solvents, process aids, intermediates, packaging materials and labelling materials.
**medical products.**
Products including, but not limited to, finished pharmaceutical products, medical devices, vaccines and in vitro diagnostics (IVDs).

**packaging material.**
Any material, including printed material, employed in the packaging of a pharmaceutical product, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

**pedigree.**
A complete record that traces the ownership of and transactions relating to a pharmaceutical product as it is distributed through the supply chain.

**pharmaceutical product.**
Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, which is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. It does not, however, include medical devices.

**product recall.**
A process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/or concerns that the product is or may be falsified. The recall might be initiated by the manufacturer, importer, wholesaler, distributor or a responsible agency.

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

**quality assurance.**
A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

**quality risk management.**
A systematic process for the assessment, control, communication and review of risks to the quality of pharmaceutical products across the product life cycle.
**quality system.**
An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

**quarantine.**
The status of pharmaceutical products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

**retest date.**
The date when a material should be re-examined to ensure that it is still suitable for use.

**sampling.**
Operations designed to obtain a representative portion of a pharmaceutical product, based on an appropriate statistical procedure, for a defined purpose, for example, acceptance of consignments or batch release.

**self-inspection.**
Self-inspection is an internal procedure followed to evaluate the entity’s compliance with GSDP and GXP in all areas of activities, designed to detect any shortcomings and to recommend and implement necessary corrective actions.

**shelf life.**
The period of time during which a pharmaceutical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf life is used to establish the expiry date of each batch.

**standard operating procedure (SOP).**
An authorized written procedure giving instructions for performing operations not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection).

**storage.**
The storing of pharmaceutical products up to the point of use.

**substandard products.**
“Substandard” medical products (also called “out of specification”) are authorized by national regulatory authorities but fail to meet either national or international quality standards or specifications – or, in some cases, both.
supplier.
A person or entity engaged in the activity of providing products and/or services.

transit.
The period during which pharmaceutical products are in the process of being carried, conveyed, or transported across, over or through a passage or route to reach the destination.

vehicles.
Trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means which are used to convey pharmaceutical products

4. GENERAL PRINCIPLES

4.1 There should be collaboration between all entities, including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of medical products to patients to ensure the quality and safety of medical products; to prevent the exposure of patients to substandard and falsified products and to ensure that the integrity of the distribution chain is maintained.

4.2 The principles of GSP and GDP should be included in national legislation and guidelines for the storage and distribution of medical products in a country or region, as applicable, as a means of establishing minimum standards. The principles of GSP and GDP are applicable to:

- medical products moving forward in the distribution chain from the manufacturer;
- medical products which are moving backwards in the chain, for example, as a result of the return or recall thereof; and
- donations of medical products.
5. QUALITY MANAGEMENT

Quality Systems

5.1 Entities involved in the storage and distribution of medical products should have a comprehensively designed, documented and correctly implemented quality system that incorporates good storage practices, good distribution practices, quality risk management principles and management review.

5.2 Senior management has the ultimate responsibility to ensure that an effective quality system is established, resourced, implemented and maintained.

5.3 The quality system should ensure that:
   - GSP and GDP are adopted and implemented to ensure that the quality of medical products is maintained throughout their shelf-life in the supply chain; medical products are appropriately procured, stored, distributed and delivered (in compliance with the legislation) to the appropriate recipients; (see 18.1)
   - operations are clearly specified in written procedures;
   - responsibilities are clearly specified in job descriptions;
   - all risks are identified, and necessary, effective controls are implemented;
   - processes are in place to assure the management of outsourced activities;
   - there is a procedure for self-inspection and quality audits;
   - there is a system for quality risk management (QRM);
   - there are systems for managing returns, complaints and recalls;
   - there are systems to manage changes, deviations and corrective and preventive actions (CAPAs).

5.4 There should be an authorized, written quality policy describing the overall intentions and requirements regarding quality. This may be reflected in a quality manual.

5.5 There should be an appropriate organizational structure. This should be presented in an authorized organizational chart. The responsibility, authority and interrelationships of personnel should be clearly indicated.

5.6 Roles and responsibilities should be clearly defined and understood by the individuals concerned and recorded as written job descriptions.

5.7 The quality system should include appropriate procedures, processes and resources.
6. QUALITY RISK MANAGEMENT

6.1 There should be a system to assess, control, communicate and review risks identified at all stages in the supply chain.

6.2 The evaluation of the risk should be based on scientific knowledge and experience and ultimately be linked to the protection of the patient.

6.3 Appropriate controls should be developed and implemented to address all risks. The effectiveness of the controls implemented should be evaluated at periodic intervals.

7. MANAGEMENT REVIEW

7.1 There should be a system for periodic management review. The review should include at least:

• senior management;
• review of the quality system and its effectiveness by using quality metrics and key performance indicators;
• identification of opportunities for continual improvement; and
• follow-up on recommendations from previous management review meetings.

7.2 Minutes and related documentation from management review meetings should be available.

8. COMPLAINTS

8.1 There should be a written procedure for the handling of complaints. In the case of a complaint about the quality of a medical product or its packaging, the original manufacturer and/or marketing authorization holder should be informed as soon as possible.

8.2 All complaints should be recorded and appropriately investigated. The root cause should be identified and the impact (e.g. on other batches or products) risk assessed. Appropriate CAPAs should be taken.

8.3 Where required, the information should be shared with the national regulatory authority and a recall initiated where appropriate.

8.4 A distinction should be made between complaints about a medical product or its packaging and those relating to distribution.
8.5 The relevant information, such as the results of the investigation of the complaint, should be shared with the relevant entities.

8.6 Medical product quality problems and suspected cases of substandard or falsified products identified should be handled according to relevant authorized procedures. The information should be shared with the manufacturer and appropriate national and/or regional regulatory authorities without delay.

9. RETURNED GOODS

9.1 Returned medical products should be handled in accordance with authorized procedures.

9.2 All returned medical products should be placed in quarantine upon receiving. The status of the goods should be clear. Precautions should be taken to prevent access and distribution until a decision has been taken with regard to their disposition. The particular storage conditions applicable to the medical products should be maintained.

9.3 Medical products returned should be destroyed unless it is certain that their quality is satisfactory after they have been critically assessed in accordance with a written and authorized procedure.

9.4 The nature of the medical product, any special storage conditions it requires, its condition and history and the time lapse since it was issued, should all be taken into account in this assessment. Where any doubt arises over the quality of the medical product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

9.5 When handling returned goods, the following considerations at least should be taken:

- A risk-based process should be followed when deciding on the fate of the returned goods. This should include, but not be limited to, the nature of the product, storage conditions, condition of the product history, time-lapse since distribution and the manner and condition of transport while being returned.
- The terms and conditions of the agreement between the parties.
- Examination of the returned goods, with decisions taken by suitably qualified, experienced and authorized persons.
9.6 Where products are rejected, authorized procedures should be followed, including safe transport.

9.7 Destruction of products should be done in accordance with international, national and local requirements regarding disposal of such products and with due consideration to the protection of the environment.

9.8 Records of all returned, rejected and destroyed medical products should be kept for a defined period in accordance with national requirements.

10. RECALLS

10.1 There should be a written procedure, in compliance with national or regional requirements, to effectively and promptly recall medical products.

10.2 The effectiveness of the procedure should be checked annually and updated as necessary.

10.3 The original manufacturer and/or marketing authorization holder, or other relevant contract party, should be informed in the event of a recall.

10.4 Information on a recall should be shared with the appropriate national or regional regulatory authority.

10.5 All recalled products should be secure, segregated, transported and stored under appropriate conditions. These should be clearly labelled as recalled products. The particular storage conditions applicable to the product should be maintained.

10.6 All customers and competent authorities of all countries to which a given medical product may have been distributed should be informed promptly of the recall of the product.

10.7 All records, including distribution records, should be readily accessible to the designated person(s) responsible for recalls. These records should contain sufficient information on products supplied to customers (e.g. name, address, contact detail, batch numbers, quantities and safety features - including exported products).

10.8 The progress of a recall process should be recorded and a final report issued which includes a reconciliation between delivered and recovered quantities of medical products.
11. **SELF-INSPECTION**

11.1 The quality system should include self-inspections. These should be conducted to monitor the implementation, compliance with and effectiveness of SOPs as well as compliance with regulations, GSP, GDP and other appropriate guidelines.

11.2 Self-inspections should be conducted periodically according to an annual schedule.

11.3 The team conducting the inspection should be free from bias and individual members should have appropriate knowledge and experience.

11.4 The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and presented to the relevant personnel and management.

11.5 Necessary CAPAs should be taken and the effectiveness of the CAPAs should be reviewed.

12. **PREMISES**

**General**

12.1 Premises should be suitably located, designed, constructed and maintained to ensure appropriate operations such as receiving, storage, picking, packing and dispatch of medical products.

12.2 There should be sufficient space, lighting and ventilation to ensure required segregation, appropriate storage conditions and cleanliness.

12.3 Sufficient security should be provided, and access should be controlled.

12.4 Appropriate controls and segregation should be provided for products requiring specific handling or storage conditions such as radioactive materials, products containing hazardous substances and products to be stored under controlled temperature and relative humidity conditions.

12.5 Receiving and dispatch bays should be separate and should protect products from weather conditions.

12.6 Activities relating to receiving and dispatch should be done in accordance with authorized procedures. Areas should be suitably equipped for the operations.
12.7 Premises should be kept clean. Cleaning equipment and cleaning agents should not become possible sources of contamination.

12.8 Premises should be protected from the entry of birds, rodents, insects and other animals. A rodent and pest control programme should be in place.

12.9 Toilets, wash, rest and canteen facilities should be separate from other areas. Food, eating, drinking and smoking should be prohibited in all areas where medical products are stored or handled.

**Receiving**

12.10 Each incoming delivery should be checked against the relevant documentation to ensure that the correct product is delivered from the correct supplier. This may include, for example, the purchase order, containers, label description, batch number, expiry date, product and quantity.

12.11 The consignment should be examined for uniformity of the containers and, if necessary, should be subdivided according to the supplier’s batch number should the delivery comprise more than one batch. Each batch should be dealt with separately.

12.12 Each container should be carefully checked for possible contamination, tampering and damage. Any suspect containers or, if necessary, the entire delivery should be quarantined for further investigation.

12.13 Receiving areas should be of sufficient size to allow the cleaning of incoming medical products.

12.14 When required, samples of medical products should be taken by appropriately trained and qualified personnel and in strict accordance with a written sampling procedure and sampling plans. Containers from which samples have been taken should be labelled accordingly.

12.15 Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.

12.16 Materials and products requiring storage under controlled conditions of temperature and relative humidity, as applicable, should be handled as a priority.

12.17 Medical products should not be transferred to saleable stock until an authorized release is obtained.
12.18 Measures should be taken to ensure that rejected medical products cannot be used. They should be segregated and securely stored while awaiting destruction or return to the supplier.

Storage areas

12.19 Precautions should be taken to prevent unauthorized persons from entering storage areas.

12.20 Storage areas should be of sufficient capacity to allow the orderly storage of the various categories of medical products.

12.21 Storage areas should be appropriately designed, constructed, maintained or adapted. They should be kept clean and there should be sufficient space and lighting.

12.22 Storage areas should be maintained within acceptable and specified temperature limits. Where special storage conditions are required on the label (e.g. temperature, relative humidity), these should be provided, controlled, monitored and recorded.

12.23 Medical products should be stored off the floor and suitably spaced to permit ventilation, cleaning and inspection. Suitable pallets should be used and kept in a good state of cleanliness and repair.

12.24 A written sanitation programme should be available indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.

12.25 There should be appropriate procedures for the clean-up of any spillage to ensure complete removal of any risk of contamination.

12.26 Where the status is ensured by storage in separate areas, these areas should be clearly marked, and their access restricted to authorized personnel. Any system replacing physical separation and labelling, or demarcation should provide equivalent security. For example, computerized systems can be used provided that they are validated to demonstrate security of access (6).

12.27 Sampling should be done under controlled conditions and conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be followed after sampling.
12.28 Certain materials and products such as highly active and radioactive materials, narcotics and other hazardous, sensitive and/or dangerous materials and products, as well as substances presenting special risks of abuse, fire or explosion (e.g. combustible liquids and solids and pressurized gases), should be stored in a dedicated area that is subject to appropriate additional safety and security measures; and in accordance with national legislation.

12.29 Medical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.

12.30 Medical products should be stored in conditions which assure that their quality is maintained. Stock should be appropriately rotated. The “first expired/first out” (FEFO) principle should be followed.

12.31 Narcotic medical products should be stored in compliance with international conventions, national laws and regulations on narcotics.

12.32 Broken or damaged items should be withdrawn from usable stock and separated.

12.33 There should be appropriate procedures for the clean-up of any spillage to ensure complete removal of any risk of contamination.

**Storage conditions**

12.34 The storage conditions for medical products should be in compliance with their labelling.

12.35 Heating, ventilation and air conditioning systems (HVAC) should be appropriately designed, installed, qualified and maintained to ensure that the required storage conditions are maintained (7).

12.36 Mapping studies for temperature and relative humidity, as appropriate, should be done (8). This applies, for example, to areas, refrigerators and freezers.

12.37 Temperature and relative humidity, as appropriate, should be controlled and monitored at regular intervals. Data should be recorded, and the records should be reviewed. The equipment used for monitoring should be calibrated and be suitable for their intended use. All records pertaining to mapping and monitoring should be kept for a suitable period of time and as required by national legislation.

**Note:** See Annex 1 for recommended storage conditions.
13. **STOCK CONTROL AND ROTATION**

13.1 Periodic stock reconciliation should be performed at defined intervals by comparing the actual and recorded stock.

13.2 The root cause for stock discrepancies should be identified and appropriate CAPAs taken to prevent recurrence.

13.3 When damaged containers are received, this should be brought to the attention of the person responsible for quality. Any action taken should be documented. (These containers should not be issued unless the quality of the medical products has been shown to be unaffected).

13.4 All stock should be checked regularly to identify obsolete, to be retested, and expired stock.

14. **EQUIPMENT**

14.1 Equipment, including computerized systems should be suitable for their intended use. These should be appropriately designed, located, installed, qualified and maintained.

14.2 Computerized systems should be capable of achieving the desired output and results.

14.3 Where electronic commerce (e-commerce) is used, i.e. electronic means for any of the steps, defined procedures and adequate systems should be in place to ensure traceability and confidence in the supply chain and products concerned.

14.4 Electronic transactions (including those conducted via the Internet) relating to the distribution of medical products should be performed only by authorized persons according to defined and authorized access and privileges.

14.5 Where GXP systems are used, these should meet the requirements of WHO and other guidelines on computerized systems (6,9).
15. QUALIFICATION AND VALIDATION

15.1 The scope and extent of qualification and validation should be determined using documented risk management principles.

15.2 Premises, utilities, equipment and instruments, processes and procedures should be considered. The scope and extent of qualification and validation in case of any significant changes should be identified.

15.3 Qualification and validation should be done following procedures and protocols. The results and outcome of the qualification and validation should be recorded in reports. Deviations should be investigated, and the completion of the qualification and validation should be concluded and approved.

16. PERSONNEL

16.1 There should be an adequate number of personnel.

16.2 Personnel should have appropriate educational qualification, experience and training relative to the activities undertaken.

16.3 Personnel should have the authority and resources needed to carry out their duties and to follow the quality systems, as well as to identify and correct deviations from the established procedures.

16.4 There should be arrangements in place to ensure that management and personnel are not subjected to commercial, political, financial and other pressures or conflict of interest that may have an adverse effect on the quality of service provided or on the integrity of medical products.

16.5 Safety procedures should be in place relating to all relevant personnel and property, environmental protection and product integrity.

16.6 Personnel should receive initial and continued training in accordance with a written training programme. The training should cover the requirements of GSP, GDP (as applicable), as well as on-the-job training. Other topics should be included, such as product security, product identification and the detection of falsified products.
16.7 Personnel dealing with hazardous products (such as highly active materials, radioactive materials, narcotics and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.

16.8 Personnel should be trained in, and observe high levels of, personal hygiene and sanitation.

16.9 Records of all training, attendance and assessments should be kept.

16.10 Personnel handling products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.

16.11 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and the clothing of personnel.

16.12 Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to medical products, must be designed and implemented to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.

16.13 Codes of practice and punitive procedures should be in place to prevent and address situations where persons involved in the storage and distribution of medical products are suspected of, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or falsifying of any product.

17. DOCUMENTATION

17.1 Documentation includes all procedures, records and data, whether in paper or electronic form. Documents should be appropriately designed, completed, reviewed, authorized, distributed and kept as required. Documents should be readily available.

17.2 Written procedures should be followed for the preparation, review, approval, use of and control of all documents relating to the policies and activities for storage and distribution of medical products process.
17.3 Documents should be laid out in an orderly fashion and be easy to complete, review and check. The title, scope, objective and purpose of each document should be clear.

17.4 The contents of documents should be accurate, legible, traceable, attributable and unambiguous.

17.5 All documents should be completed, signed and dated as required by authorized person(s) and should not be changed without the necessary authorization.

17.6 Documentation should be prepared and maintained in accordance with the national legislation and principles of good documentation practices (9).

17.7 Data should meet ALCOA principles. Procedures should be followed, and records maintained for the back-up and restoration of data.

17.8 The distributor must establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation.

17.9 Documents should be reviewed regularly and kept up-to-date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

17.10 All records should be stored and retained using facilities that prevent unauthorized access, modification, damage, deterioration and/or loss of documentation during the entire life cycle of the record. Records must be readily retrievable.

17.11 Comprehensive records should be maintained for all receipts, storage, issues and distribution. The records should include, for example:

- date (e.g. receipt or dispatch, as appropriate);
- name and description of the product;
- quantity received, or supplied;
- name and address of the supplier and customer.
- batch number(s);
- expiry date;
- suitability of the supplier;
- qualification of suppliers; and
- customer qualification.
17.12 All containers should be clearly labelled with at least the name of the medical product, batch number, expiry date or retest date, and the specified storage conditions.

18. ACTIVITIES AND OPERATIONS

18.1 All activities and operations should be conducted in accordance with national legislation, GSP, GDP and associated guidelines.

18.2 Storage and distribution of medical products should be done by persons so authorized, in accordance with national legislation.

18.3 Activities and operations should be performed in accordance with documented procedures.

18.4 Automated Storage and Retrieval Systems (AS/RS) and operations should comply with current GSP, GDP and GXP guidelines, as well as the recommendations in this guideline.

Receiving

18.5 Medical products should be procured from appropriately authorized suppliers.

18.6 Deliveries should be examined for damage, seal intactness, signs of tampering, labelling, completeness of order and other related aspects, at the time of receiving.

18.7 Containers and consignments not meeting acceptance criteria at the time of receipt should be labelled, kept separate and investigated. This includes suspected falsified products.

Storage

18.8 Medical products requiring specific storage conditions, or controlled access, (e.g. narcotics) should be processed without delay and stored in accordance with their requirements.

18.9 Appropriate controls should be implemented to prevent contamination and/or mix ups during storage.

18.10 Controls and procedures should be in place to prevent and handle spillage and breakage.
Repackaging and relabelling

18.11 Repackaging and relabelling of materials and products are not recommended. Where repackaging and relabelling occur, these activities should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international requirements, and in accordance with GMP.

18.12 Procedures should be in place for the controlled disposal of original packaging to prevent re-use thereof.

Distribution and transport

18.13 Medical products should be transported in accordance with the conditions stated on the labels. There should be no risk to the quality of the medical product during transport and distribution.

18.14 Product, batch and container identity should be maintained at all times.

18.15 All labels should remain legible.

18.16 Distribution records should be sufficiently detailed to allow for a recall when required.

18.17 Drivers of vehicles should be identified and present appropriate documentation to demonstrate that they are authorized to transport medical products.

18.18 Vehicles should be suitable for their purpose, with sufficient space and appropriately equipped to protect medical products.

18.19 The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of the products.

18.20 Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security and traceability of vehicles with products.

18.21 Where possible, dedicated vehicles and equipment should be used for medical products. Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the products will not be compromised. Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.
18.22 There should be procedures in place for the operation and maintenance of all vehicles and equipment.

18.23 Equipment and materials used for the cleaning of vehicles should not become a source of contamination or have an adverse effect on product quality.

18.24 Appropriate environmental conditions should be maintained, monitored and recorded. All monitoring records should be kept for a defined period of time as required by national legislation. Records of monitoring data should be made available for inspection by the regulatory or other oversight body.

18.25 Instruments used for monitoring conditions, for example, temperature and humidity, within vehicles and containers should be calibrated at regular intervals.

18.26 Rejected, recalled and returned products, as well as those suspected as being falsified, should be securely packaged, clearly labelled and be accompanied by the appropriate supporting documentation.

18.27 Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.

18.28 Shipment containers should have no adverse effect on the quality of the medical products and should offer adequate protection to materials and these products. Containers should be labelled indicating, for example, handling and storage conditions, precautions, contents and source, and safety symbols, as appropriate.

18.29 Special care should be taken when using dry ice and liquid nitrogen in shipment containers due to safety issues and possible adverse effects on the quality of medical products.

18.30 Written procedures should be available for the handling of damaged and/or broken shipment containers. Particular attention should be paid to those containing potentially toxic and hazardous products.
Dispatch

18.31 There should be documented, detailed procedures for the dispatch of products.

18.32 Medical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national legislation. Written proof of such authorization must be obtained prior to the distribution of products to such persons or entities.

18.33 Dispatch and transportation should be undertaken only after the receipt of a valid order which should be documented.

18.34 Records for the dispatch of products should be prepared and should include information such as, but not limited to:

- date of dispatch;
- complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number, names of contact persons;
- status of the addressee (e.g. retail pharmacy, hospital or community clinic);
- a description of the products including, for example, name, dosage form and strength (if applicable);
- quantity of the products, i.e. number of containers and quantity per container (if applicable);
- applicable transport and storage conditions;
- a unique number to allow identification of the delivery order; and
- assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt to facilitate traceability).

18.35 Records of dispatch should contain sufficient information to enable traceability of the product. Such records should facilitate the recall of a batch of a product, if necessary, as well as the investigation of falsified or potentially falsified products. In addition, the assigned batch number and expiry date of products should be recorded at the point of receipt to facilitate traceability.

18.36 Vehicles and containers should be loaded carefully and systematically on a last-in/first-out (LIFO) to save time when unloading, to prevent physical damage and to reduce security risks. Extra care should be taken during loading and unloading of cartons to avoid damage.
18.37 Medical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to be reached before the products are used by the consumer (10).

18.38 Medical products and shipment containers should be secured in order to prevent or to provide evidence of unauthorized access. Vehicles and operators should be provided with additional security where necessary, to prevent theft and other misappropriation of products during transportation.

18.39 Medical Products should be stored and transported in accordance with procedures such that:

- the identity of the product is not lost;
- the product does not contaminate and is not contaminated by other products;
- adequate precautions are taken against spillage, breakage, misappropriation and theft; and
- appropriate environmental conditions are maintained, for example, using cold chain for thermolabile products.

18.40 Written procedures should be in place for investigating and dealing with any failure to comply with storage requirements, for example, temperature deviations. If a deviation has been noticed during transportation by the person or entity responsible for transportation, this should be reported to the distributor and recipient. In cases where the recipient notices the deviation, it should be reported to the distributor.

18.41 Transportation of products containing hazardous substances or narcotics and other dependence-producing substances, should be transported in safe, suitably designed, secured containers and vehicles. In addition, the requirements of applicable international agreements and national legislation should be met.

18.42 Spillages should be cleaned up as soon as possible in order to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.

18.43 Damage to containers and any other event or problem that occurs during transit must be recorded and reported to the relevant department, entity or authority and investigated.

18.44 Products in transit must be accompanied by the appropriate documentation.
19. **OUTSOURCED ACTIVITIES**

19.1 Any activity relating to the storage and distribution of a medical product which is delegated to another person or entity should be performed by the parties appropriately authorized in accordance with national legislation and the terms of a written contract.

19.2 There should be a written contract between the entities. The contract should define the responsibilities of each entity (contract giver and contract acceptor) and cover at least the following:

- compliance with this guideline and the principles of GSP and GDP;
- responsibilities of all entities for measures to avoid the entry of substandard and falsified products into the distribution chain;
- training of personnel;
- conditions of subcontracting subject to the written approval of the contract giver; and
- periodic audits.

19.3 The contract giver should assess the competence of the contract acceptor before entering into the contract.

19.4 The contract giver should provide all relevant information relating to the material/products to the contract acceptor.

19.5 The contract acceptor should have adequate resources (e.g. premises, equipment, personnel, knowledge, experience and vehicles, as appropriate) to carry out the work.

19.6 The contract acceptor should refrain from performing any activity that may adversely affect the materials or products handled.

20. **SUBSTANDARD AND FALSIFIED PRODUCTS**

20.1 The quality system should include procedures to assist in identifying and handling medical products that are suspected to be substandard and/or falsified.

20.2 Where such medical products are identified, the holder of the marketing authorization, the manufacturer and the appropriate national, regional and international regulatory bodies (as appropriate), as well as other relevant competent authorities, should be informed.
20.3 Such products should be stored in a secure, segregated area and clearly identified to prevent further distribution or sale. Access should be controlled.

20.4 Records should be maintained reflecting the investigations and action taken, such as disposal of the product. Falsified products should not re-enter the market.

21. **INSPECTION OF STORAGE AND DISTRIBUTION FACILITIES**

21.1 Storage and distribution facilities should be inspected by inspectors so authorized by national legislation. This should be done at determined, periodic intervals.

21.2 Inspectors should have appropriate educational qualifications, knowledge and experience (II).

21.3 An inspection should normally be conducted by a team of inspectors.

21.4 Inspectors should assess compliance with national legislation, GSP, GDP and related guidelines (GXP) as appropriate.

21.5 Inspections should cover the premises, equipment, personnel, activities, quality system, qualification and validation and other related aspects as contained in this guideline.

21.6 An inspection report should be prepared and provided to the inspected entity within a defined period of time from the last day of the inspection. Observations may be categorized based on risk assessment.

21.7 CAPA for observations listed as non-compliances in the inspection report, with the national legislation and guidelines, should be submitted for review by the inspectors within the defined period as stated by the inspectors.

21.8 Inspections should be closed with a conclusion after the review of the CAPAs.
References


Further reading


ANNEX 1
RECOMMENDED STORAGE CONDITIONS

Note: Appropriate conditions should be provided for medical products during storage and distribution. Conditions should be maintained as stated on their labels from the manufacturers and suppliers during storage and distribution. Statements such as “store at ambient conditions” should be avoided. Where possible, actual limits should be specified by the manufacturers, such as “store below 25°C”. See Table 1 below.

Table 1. Recommended limits for descriptive storage conditions

<table>
<thead>
<tr>
<th>Label description</th>
<th>Recommended limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store at controlled room temperature</td>
<td>15 to 25 °C</td>
</tr>
<tr>
<td>Store in a cold or cool place</td>
<td>8 to 15 °C</td>
</tr>
<tr>
<td>Store in a refrigerator</td>
<td>5 ± 3 °C</td>
</tr>
<tr>
<td>Store in a freezer</td>
<td>-20 ± 5 °C</td>
</tr>
<tr>
<td>Store in deep freezer</td>
<td>Below -15 °C or -70 ±10 °C</td>
</tr>
<tr>
<td>Store in a dry place</td>
<td>No more than 60% relative humidity</td>
</tr>
<tr>
<td>Protect from moisture</td>
<td>No more than 60% relative humidity</td>
</tr>
<tr>
<td>Store under ambient conditions</td>
<td>Store in dry, well-ventilated premises at temperatures of between 15 –30 °C. Extraneous odours, other indications of contamination and intense light must be excluded.</td>
</tr>
<tr>
<td>Protect from light</td>
<td>To be provided in light resistant containers. Light level not exceeding 500 lux.</td>
</tr>
<tr>
<td>Chilled</td>
<td>Refrigerated</td>
</tr>
</tbody>
</table>

1These limits are recommended values and are based on pharmacopoeia limits and guidelines.
The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2019.

Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 September 2019. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the January 2020 version of the ATC/DDD Index.

New ATC 5th level codes:

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
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<td>A02BC08</td>
</tr>
<tr>
<td>homatropine methylbromide</td>
<td>A03BB06</td>
</tr>
<tr>
<td>bempedoic acid</td>
<td>C10AX15</td>
</tr>
<tr>
<td>rosuvastatin and fenofibrate</td>
<td>C10BA09</td>
</tr>
<tr>
<td>rosuvastatin and ramipril</td>
<td>C10BX17</td>
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<tr>
<td>rifamycin</td>
<td>D06AX15</td>
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<tr>
<td>econazole, combinations</td>
<td>G01AF55</td>
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<tr>
<td>osilodrostat</td>
<td>H02CA02</td>
</tr>
<tr>
<td>sarecycline</td>
<td>J01AA14</td>
</tr>
<tr>
<td>omadacycline</td>
<td>J01AA15</td>
</tr>
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<td>imipenem, cilastatin and beta-lactamase inhibitor</td>
<td>J01DH56</td>
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<tr>
<td>lefamulin</td>
<td>J01XX12</td>
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<tr>
<td>darunavir and ritonavir</td>
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</tr>
<tr>
<td>lamivudine, tenofovir disoproxil and dolutegravir</td>
<td>J05AR27</td>
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<td>fremanezumab</td>
<td>N02CD03</td>
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<tr>
<td>remimazolam</td>
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</tr>
<tr>
<td>indacaterol and mometasone</td>
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<tr>
<td>formoterol and tiotropium bromide</td>
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<tr>
<td>formoterol, glycopyrronium bromide and budesonide</td>
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<tr>
<td>indacaterol, glycopyrronium bromide and mometasone</td>
<td>R03AL12</td>
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<td>revefenacin</td>
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<td>voretigene neparvovec</td>
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<td>folic acid</td>
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<td>methacholine</td>
<td>V04CX03</td>
</tr>
<tr>
<td>mannitol</td>
<td>V04CX04</td>
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<tr>
<td>$^{13}$C-urea</td>
<td>V04CX05</td>
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<td>hexaminolevulinate</td>
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<tr>
<td>edrophonium</td>
<td>V04CX07</td>
</tr>
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<td>carbon monoxide</td>
<td>V04CX08</td>
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<tr>
<td>patent blue</td>
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1) New ATC 4th level, N02CD Calcitonin gene-related peptide (CGRP) antagonists

### New ATC level codes (other than 5th levels):

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<td>Calcitonin gene-related peptide (CGRP) antagonists</td>
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### Change of ATC level codes:

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<td>P01CX04</td>
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<tr>
<td>erenumab</td>
<td>N02CX07</td>
<td>N02CD01</td>
</tr>
<tr>
<td>galcanezumab</td>
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### Change of ATC level names:

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<td>homatropine methylbromide and psycholeptics</td>
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<td>B06AB</td>
<td>Other hem products</td>
<td>Heme products</td>
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<td>B06AB01</td>
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### New DDDs:

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<td>V</td>
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<td>g</td>
<td>O</td>
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<td>omadacycline</td>
<td>0.3</td>
<td>g</td>
<td>O</td>
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<td>doravirine</td>
<td>0.1</td>
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<td>O</td>
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</table>

1) ATC code altered from N02CX08. New ATC 4th level N02CD valid from January 2020.
2) New ATC 4th level N02CD valid from January 2020.

WHO Collaborating Centre for Drug Statistics Methodology
Oslo, May 2019
ATC/DDD Classification (Final)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2018.

These are considered as final and will be included in the January 2020 version of the ATC/DDD Index.

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<td>vonoprazan, amoxicillin and clarithromycin</td>
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<td>vonoprazan, amoxicillin and metronidazole</td>
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<td>opinercept</td>
<td>L04AB07</td>
</tr>
<tr>
<td>risankizumab</td>
<td>L04AC18</td>
</tr>
<tr>
<td>esketamine</td>
<td>N06AX27</td>
</tr>
<tr>
<td>solriamfetol</td>
<td>N06BA14</td>
</tr>
<tr>
<td>inotersen</td>
<td>N07XX15</td>
</tr>
<tr>
<td>tafenoquine</td>
<td>P01BA07</td>
</tr>
<tr>
<td>moxidectin</td>
<td>P02CX03</td>
</tr>
<tr>
<td>vancomycin</td>
<td>S01AA28</td>
</tr>
<tr>
<td>latanoprostene bunod</td>
<td>S01EE06</td>
</tr>
<tr>
<td>latanoprost and netarsudil</td>
<td>S01EE51</td>
</tr>
<tr>
<td>brolicizumab</td>
<td>S01LA06</td>
</tr>
<tr>
<td>arginine and lysine</td>
<td>V03AF11</td>
</tr>
<tr>
<td>methionine ($^{11}$C)</td>
<td>V09IX13</td>
</tr>
</tbody>
</table>

1) New ATC 4th level, B06AX Other hematological agents

2) Nasal formulations indicated for major depressive disorders. Parenteral formulations are classified in N01AX14.
New ATC level codes (other than 5\textsuperscript{th} levels):

| Other hematological agents | B06AX |

Change of ATC level names:

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactobacillus fermentum</td>
<td>lactobacillus</td>
<td>G01AX14</td>
</tr>
<tr>
<td>microspheres of human albumin</td>
<td>perflutren, human albumin microspheres</td>
<td>V08DA01</td>
</tr>
<tr>
<td>microspheres of phospholipids</td>
<td>perflutren, phospholipid microspheres</td>
<td>V08DA04</td>
</tr>
<tr>
<td>sulfur hexafluoride</td>
<td>sulfur hexafluoride, phospholipid microspheres</td>
<td>V08DA05</td>
</tr>
<tr>
<td>perflubutane polymer microspheres</td>
<td>perflubutane, phospholipid microspheres</td>
<td>V08DA06</td>
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</table>

New DDDs:

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm.R</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>nabilone</td>
<td>3</td>
<td>mg</td>
<td>O</td>
<td>A04AD11</td>
</tr>
<tr>
<td>semaglutide</td>
<td>0.11</td>
<td>mg</td>
<td>P</td>
<td>A10BJ06</td>
</tr>
<tr>
<td>cerliponase alfa</td>
<td>21</td>
<td>mg</td>
<td>P</td>
<td>A16AB17</td>
</tr>
<tr>
<td>glycerol phenylbutyrate</td>
<td>15</td>
<td>g</td>
<td>O</td>
<td>A16AX09</td>
</tr>
<tr>
<td>pentosan polysulfate sodium</td>
<td>0.3</td>
<td>g</td>
<td>O</td>
<td>G04BX15</td>
</tr>
<tr>
<td>cefpodoxime and beta-lactamase inhibitor</td>
<td>0.4</td>
<td>g\textsuperscript{i}</td>
<td>O</td>
<td>J01DD64</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>0.24</td>
<td>g</td>
<td>Inhal.solution</td>
<td>J01MA12</td>
</tr>
<tr>
<td>calcium aminosalicylate</td>
<td>15</td>
<td>g</td>
<td>O</td>
<td>J04AA03</td>
</tr>
<tr>
<td>enniomycin</td>
<td>1</td>
<td>g</td>
<td>P</td>
<td>J04AB06</td>
</tr>
<tr>
<td>vidarabine</td>
<td>0.7</td>
<td>g</td>
<td>P</td>
<td>J05AB03</td>
</tr>
<tr>
<td>peramivir</td>
<td>0.6</td>
<td>g</td>
<td>P</td>
<td>J05AH03</td>
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<tr>
<td>laninamivir</td>
<td>40</td>
<td>mg</td>
<td>Inhal.powder</td>
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<tr>
<td>asunaprevir</td>
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<td>g</td>
<td>O</td>
<td>J05AP06</td>
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<tr>
<td>elbasvir</td>
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<td>mg</td>
<td>O</td>
<td>J05AP10</td>
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<tr>
<td>grazoprevir</td>
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<td>g</td>
<td>O</td>
<td>J05AP11</td>
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<tr>
<td>amenamevir</td>
<td>0.4</td>
<td>g</td>
<td>O</td>
<td>J05AX26</td>
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<tr>
<td>favipiravir</td>
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<td>g</td>
<td>O</td>
<td>J05AX27</td>
</tr>
<tr>
<td>apalutamide</td>
<td>0.24</td>
<td>g</td>
<td>O</td>
<td>L02BB05</td>
</tr>
</tbody>
</table>
### ATC level name/INN

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm.R</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opinercept</td>
<td>7</td>
<td>mg</td>
<td>P</td>
<td>L04AB07</td>
</tr>
<tr>
<td>brodalumab</td>
<td>15</td>
<td>mg</td>
<td>P</td>
<td>L04AC12</td>
</tr>
<tr>
<td>pridinol</td>
<td>6</td>
<td>mg</td>
<td>O</td>
<td>M03BX03</td>
</tr>
<tr>
<td>erenumab</td>
<td>2.5</td>
<td>mg</td>
<td>P</td>
<td>N02CD01</td>
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<tr>
<td>sodium zirconium cyclosilicate</td>
<td>7.5</td>
<td>g</td>
<td>O</td>
<td>V03AE10</td>
</tr>
</tbody>
</table>

1) Refers to cefpodoxime. Decided at the meeting in the WHO ATC/DDD Working Group in March 2018.
2) ATC code altered from N02CX07. New ATC 4th level N02CD Calcitonin gene-related peptide (CGRP) antagonists valid from January 2020.

### Changes of DDDs:

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous DDD</th>
<th>New DDD</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>liraglutide</td>
<td>1.2 mg P</td>
<td>1.5 mg P</td>
<td>A10BJ02</td>
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</tbody>
</table>

WHO Collaborating Centre for Drug Statistics Methodology
Oslo, May 2019

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