

# WHO Drug Information

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### Abbreviations and websites

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

**Note:**

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

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# Regulatory Requirements

## An Assessment of Global Chemistry, Manufacturing and Controls (CMC) Regulatory Requirements in Low and Middle Income Countries

The new Director General of the World Health Organization has stated that one of his top priorities is “Health for all” saying that “*ensuring universal health coverage without impoverishment is the foundation for achieving the health objectives of the Sustainable Development Goals – because when people are healthy, their families, communities, and countries benefit.*” He emphasized that “[the WHO’s] top priority must be to support national health authorities’ efforts to strengthen all the building blocks of health systems and to enact policies aimed at ensuring health care is equitable and affordable for all.”

(<http://www.who.int/dg/en/>)

### **The issue – It is challenging to locate and interpret the regulatory requirements of many low and middle income (LMIC) countries**

Access to quality health care means access to high quality, affordable health care products. This is consistent with Sustainable Development Goal #3.8 of the United Nations (<http://www.who.int/sdg/targets/en/>), which emphasizes the promotion of health through expanded access to quality assured medicines and other health care products. The manufacturing controls and quality assurance systems, including international good manufacturing practices, are the foundation for assuring that the health care products used by patients and practitioners around the world are quality products which they can depend to improve and often save lives.

Knowing the relevant manufacturing control requirements and the systems by which they are enforced in various countries is fundamental to the production of quality health care products. However, easy access to such up-to-date information for low-income countries has been challenging. Lack of easy access to regulations and their consistent interpretation often increased the time and costs of developing and producing medicines for these markets.

A significant portion of the global burden of disease is borne by LMIC with HIV/AIDS, malaria, and tuberculosis (TB) among the deadliest diseases. In 2013, the WHO reported 35 million people were infected with HIV/AIDS, 97 countries reported ongoing malaria transmission, and 8.6 million new cases of TB occurred.

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<sup>2</sup> PricewaterhouseCoopers (PwC)

Unfortunately it is in the LMICs where navigating the local regulatory requirements governing registration of medicines can be the most challenging. Frequently the chemistry, manufacturing, and controls (CMC) requirements are especially difficult to locate and interpret for many LMICs. In addition, the requirements can often vary significantly between LMICs making it difficult for organizations trying to develop the same drug for different countries. Enforcement is equally challenging as LMICs have varying levels of regulatory maturity and consistency.

Many manufacturers marketing medicines that treat these deadly diseases use programmes such as the WHO's Prequalification Programme (PQ) or the US Food and Drug Administration's PEPFAR Tentative Approval pathway to help facilitate national drug registration. Manufacturers still need to obtain approval from each individual LMICs' National Regulatory Authority (NRA) through a) individual country product registration application; b) a facilitated pathway like the WHO Collaborative Registration Procedure; or c) often times an application through both processes to minimize risk and accelerate approvals<sup>1</sup>.

Each LMIC registration helps assure that products entering these markets are safe, efficacious and meet the requisite manufacturing quality standards. Manufacturers must comply not only with the requirements governing the regulatory pathways that allow a medicine to reach the market in LMIC countries, but must also consider often complex import/export requirements such as import licenses, marketing authorization holder restrictions and quality laboratory control testing at import. Import/export requirements are often more significant for medicines developed for

LMICs because they are typically manufactured in low cost manufacturing countries such as China and India, to ensure they can be made economically. Finally, for many of these markets, products are purchased by national or international procurement agencies, which not infrequently have their own requirements that affect the manufacturing and packaging of these products.

**The Implication – The lack of visibility of regulatory requirements in LMIC can result in higher costs and patients' delayed access to drugs.**

Manufacturers encounter CMC issues at a high frequency both in developed and emerging markets. Even though manufacturers generally have extensive experience and good visibility into the regulation of more established and well-resourced Regulatory Authorities such as the US FDA and European Medicines Agency (EMA) or WHO PQ, literature is replete with assessments of CMC deficiencies within registration dossiers submitted through these pathways<sup>4</sup>. The extent to which companies encounter CMC issues in these more established pathways is illustrated by studies into Active Pharmaceutical Ingredient Master Files (APIMF) and registration dossiers submitted by generic manufacturers to the WHO PQ programme. In one study it was found that over a six-year period, half of APIMF had CMC deficiencies, with the most critical related to the specific manufacturing process and the key materials used (API starting material), which impact the API impurities content<sup>2</sup>. Similarly, a study of generic product dossiers submitted to the WHO PQ programme over a three-year period identified deficiencies in 147 of 162 dossiers assessed. The most common

issues included incomplete / inaccurate API and finished pharmaceutical products (FPP) specifications, deficiencies in FPP manufacturing process and controls, unacceptable comparator product, insufficient stability data (months and batches), and submission without bioequivalence or biowaiver data<sup>3</sup>.

CMC issues can be even more challenging in LMICs due to the lack of awareness of all the regulatory requirements. Currently there is no single publicly available repository that comprehensively captures the registration and CMC requirements of LMICs. Therefore, the regulatory teams within manufacturers undertake the time-consuming task of locating and interpreting LMIC's requirements for each country in which they want to introduce their products. Many times, members of these regulatory teams need to ask the NRAs for clarifications, and must continually monitor the relevant publications and websites, if they exist, for regulatory changes that impact their products. In addition, the way NRAs interpret their regulations can also change over time as they gain more experience with the medicines. These efforts can put considerable pressure on smaller organizations and Product Development Partnerships<sup>a</sup> with limited resources that are focused on global health drugs.

Issues that manufacturers face in navigating and complying with CMC requirements to obtain regulatory approval in LMICs are highlighted in numerous publications. They include the need for certification of documentation from the country of origin,

Good Manufacturing Practices (GMP) certificates from specific or multiple countries, and restrictions on the use of specific raw materials<sup>4, 5, 6, 7, 8, 9</sup>.

Manufacturer's efforts to comply with these requirements often create delays and increase the cost of pharmaceutical development. Examples of challenges that were encountered in product introduction of global health medicines among Product

Development Partnerships include:

- **Stability studies** – During product registration, the marketing authorization holder needs to provide evidence of the stability of the product in local climatic conditions. Stability studies are essential to ensure adequate shelf life during clinical testing and for assigning appropriate expiration timing for the drug product. Different LMICs may have different requirements for demonstrating stability. Some partners faced challenges when their stability studies during development only accounted for climatic zones of the first wave of countries planned for product registration. Subsequently the manufacturer had to repeat stability studies under new conditions once they realized the original data would not be acceptable in some LMICs. The lack of upfront visibility into the required stability study conditions delayed product introduction in some LMICs by at least 6 months and added additional costs.
- **GMP Inspections** – Delays in the scheduling of GMP inspections by LMIC NRAs, often a requirement for product

<sup>a</sup> Product Development Partnerships (PDP) are a type of public private partnership that focuses on developing innovative technologies to address high-burden diseases in low- and middle-income countries. PDPs work across the product development life-cycle partnering with private sector, academic institutions, governments, foundations and multi-lateral organizations to develop and deliver new health solutions.

approval, have led to delayed product introduction from months to years in some countries. This delay occurs despite manufacturers having a valid GMP certificate from WHO and/or a well-resourced NRA for the same product produced on the same manufacturing line as intended for the new market. The issue is compounded by a lack of visibility into the timeline for GMP inspection by LMICs and also unclear country-specific requirements when using a facilitated pathways such as WHO CRP.

- **Labeling** - Varying requirements by country including language and content of the label need to be managed both for initial product approval and for the lifetime of the product as variations to the label are enacted.
- **Packaging** – Initial introduction of a global health product can be delayed and involve additional costs as manufacturers navigated different packs sizes for different countries – some countries allowed full treatment packs while others would only accept monthly packs to facilitate reimbursement. In addition, procurers often have specifications for pack size in order for a product to be eligible for purchase.
- **In-country QC testing** – Provision of samples, reference standards, working standards, columns and other testing materials at registration often delayed product introduction and added costs. Particularly, the requirement for a large number of samples with sufficient product shelf life for testing at registration can be costly if not planned ahead of time.
- **Prior NRA Marketing Authorization** – The requirement for a Certificate of Pharmaceutical Product (CPP) for many

LMICs, which generally has to be notarized or apostilled can add significant time and complexity to product introduction and maintenance of marketing authorization throughout the lifetime of the product.

- **Reference Product Selection** – Some countries have specific requirements regarding the use of local comparators for bioequivalence studies, where the study should be conducted or which international comparator would be accepted. Manufacturers have experienced delays and added costs because they did not have visibility into some of these requirements early during product development.

In many of the cases discussed above, an easily accessible, integrated and clear view of requirements across all target countries for product introduction would have facilitated planning and mitigated these challenges. Specifically, manufacturers with access to the information can better sequence CMC activities such as stability studies, bioequivalence studies, GMP inspection, manufacturing of samples for registration, design of labels and packaging, and obtain/authenticate CPP to minimize delays and costly reworks. A solution that provides visibility and clarity into LMIC requirements can therefore potentially accelerate product introduction, reduce costs and saves lives.

## Our solution – A publicly available CMC regulatory database that covers 75 LMICS<sup>b</sup>

To address varying regulatory requirements and promote the timely delivery of economical, high-quality, approved medicines for use in LMICs, a global health partnership has created a database<sup>b</sup> of the CMC regulatory requirements for small molecules for 75 LMICs that have a high public health burden. The selection criteria for countries included a) large MICs with a drug substance or drug product manufacturing base, b) select participants of the WHO Collaborative Registration Procedure, c) priority global health countries using Gavi eligible countries as a proxy, or d) additional priority global health countries as determined in a survey completed by key Product Development Partnerships.

The output is an increasingly reliable and comprehensive source of up-to-date information for the CMC and registration regulatory requirements, which are critical for the efficient development of new medicines for underserved markets.

The data gathered for the repository were structured based on the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use's Module 3 of the Common Technical Document. The contents of the database include procedural and administrative requirements, submission pathways and approvals for both clinical and commercial manufacturing of API and FPP in the context of local manufacturing use, and export and import requirements by country as shown in Figure 1.

**Figure 1: The database is structured based on these three domains**

	Example requirements	
<b>1 Prerequisites &amp; administrative requirements</b>	<ul style="list-style-type: none"> <li>No objection certificate issued by Central License Authority (India)</li> <li>Form 29 as issued by State Licensing Authority (India)</li> </ul>	<ul style="list-style-type: none"> <li>Specific requirements to source materials for clinical manufacturing</li> <li>Storage requirements for clinical supplies</li> <li>Import &amp; export requirements</li> </ul>
<b>2 CMC requirements for clinical &amp; commercial manufacturing</b>	<ul style="list-style-type: none"> <li>Batch size/quantity for clinical supplies, registration, and validation</li> <li>Stability study requirements / environmental conditions (e.g., ACC, CRT, Zone IV etc.)</li> <li>API and excipient requirement</li> </ul>	<ul style="list-style-type: none"> <li>Manufacturing facility requirements for clinical/registration batches</li> <li>Process validation requirements</li> <li>Facility cGMP approval and inspection requirements</li> </ul>
<b>3 CMC requirements for product registration (Dossier submission)</b>	<ul style="list-style-type: none"> <li>Specific regional information</li> <li>Executed batch records</li> <li>Documents (chromatograms, CoAs, etc.)</li> </ul>	<ul style="list-style-type: none"> <li>Safety requirements</li> <li>Comparability protocol</li> <li>Validation package</li> </ul>

<sup>b</sup> The database is in pilot phase and broader access will be available once the tool is transitioned to the commercial partner, Clarivate Analytics, and web-enabled.

The data was compiled through a combination of desk research of published NRA requirements and interviews with regulatory practitioners from the LMICs, pharmaceutical companies and multilateral organizations. Efforts are currently underway to work with individual countries to validate the data for their country in the database. These interviews enabled the documentation of real-life experiences

interpreting and navigating the various LMIC regulations, which can differ from the words used in the published regulation. The functionality of the database includes a schematic of the regulatory pathway by country. The search functionality includes a view of requirements by country and comparisons across countries and requirements.

**Figure 2: The database covers 75 LMICs across Africa, Asia, the Commonwealth of Independent States, Latin America and the Caribbean**



### **Conclusion – Potential impact of increased visibility into LMIC CMC regulatory requirements for manufacturers, NRAs, and the global health community**

The database provides visibility into the consolidated CMC requirements across target LMIC and provides manufacturers with the information to better plan and sequence CMC activities to minimize the challenges and impact of varied LMIC

requirements. Through this effort, for the first time, the drug development community will be able to get information to create a product development strategy by accessing 75 LMIC CMC regulatory requirements for small molecules in one database. The information should enable developers and manufacturers to optimize the delivery of medicines to LMICs through advanced planning for unique local requirements and through the sequencing of regulatory activities to expedite approvals.

The database also provides information that LMIC NRAs can evaluate and compare their requirements with those of similarly situated NRAs so as to potentially leverage these alternative approaches that could maintain the quality and safety of medicines while not jeopardizing timely patient access to essential or innovative medicines. The visibility into the type and prevalence of divergent country-specific requirements provides organizations that develop global health medicines with an opportunity to build on the database to identify potential solutions to facilitate the introduction of new drugs. This database could also help with

efforts aimed at harmonizing and streamlining local, regional or global regulatory requirements to accelerate the development and delivery of life-saving quality-assured global health medicines to vulnerable populations. A new web-based CMC Database is being designed and developed by a commercial partner, Clarivate Analytics. The database will provide access to LMICs, WHO and select procurement agencies at no-cost by the end of 2018 and will be commercially available in 2019. 

#### References:

- <sup>1</sup> Caturla Goñi, Mercè. "Accelerating regulatory approvals through the World Health Organization collaborative registration procedures." *Pharmaceuticals Policy and Law* 18.1-4 (2016): 109-120.
- <sup>2</sup> Diego, Isabel Ortega, et al. "Review of Quality Deficiencies Found in Active Pharmaceutical Ingredient Master Files Submitted to the WHO Prequalification of Medicines Programme." *Journal of Pharmacy & Pharmaceutical Sciences* 17.2 (2014): 169-186.
- <sup>3</sup> Worku, Wondiyfraw Z., et al. "Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme." *Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector* 9.2 (2012): 63-74.
- <sup>4</sup> Huang, Baobin, et al. "Technical gaps faced by Chinese generic medicine manufacturers to achieve the standards of WHO medicines Prequalification." *Journal of Generic Medicines: The Business Journal for the Generic Medicines Sector* 10.1 (2013): 14-21.
- <sup>5</sup> Flary, N, et al. "Comparison of generic drug registration requirements in ASEAN countries." *International Journal of Research in Pharmacy and Chemistry* (2015): 145-149.
- <sup>6</sup> Prat, Adriana G. "A practical overview of requirements for drug registration in Latin America." *Regulatory Rapporteur* 10.9 (2013): 5-10.
- <sup>7</sup> Wileman, Harriet, and Arun Mishra. "Drug lag and key regulatory barriers in the emerging markets." *Perspectives in clinical research* 1.2 (2010): 51
- <sup>8</sup> Hill, Suzanne, and Kent Johnson. *Emerging challenges and opportunities in drug registration and regulation in developing countries*. Department for International Development, 2004.
- <sup>9</sup> Moran, Mary, et al. "Registering new drugs for low-income countries: the African challenge." *PLoS Med* 8.2 (2011): e1000411.



## Consultation documents

To receive draft monographs by email please contact Ms Sinead Jones (jonessi@who.int), stating that you wish to be added to the electronic mailing list.

### *The International Pharmacopoeia*

#### Limit Test for Heavy Metals

This is a draft proposal of revision for *The International Pharmacopoeia* (Working document QAS/18.769). The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

**[Note from the Secretariat:** Feedback is being sought in relation to the revision of the method of analysis 2.2.3 Limit Test for Heavy Metals. It is proposed to change the provision as follows:

- to add a note to provide users of the International Pharmacopoeia with the option to apply ICH Q3D principles to control elemental impurities;
- to add a new procedure for the preparation of the test solution: procedure 5, a closed-vessel microwave digestion that shall be used as an alternative, in particular, for procedures 3 and 4 employing ignition techniques (in new and revised monographs, procedure 5 shall be preferred to procedures 3 or 4);
- to replace the reagent hydrogen sulfide R by thioacetamide R; and
- to align parts of text to the corresponding text included in the European Pharmacopoeia (2.1.8), thereby keeping and further simplifying the structure of the existing text.

In the text available at the above-mentioned website, changes from the current monograph are indicated in the text by insert or ~~delete~~.

**Note:** The Guideline for Elemental Impurities Q3D, published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), presents a process to assess and control elemental impurities in finished pharmaceutical products using the principles of risk assessment. It is within a regulatory authority's remit to decide whether or not they apply this guideline for the assessment of elemental impurities. If ICH Q3D is implemented, compliance of pharmaceutical substances with the limit test for heavy metals will no longer be required.

The limit test for heavy metals is provided to demonstrate that the content of metallic impurities that are precipitated as coloured sulfides by thioacetamide does not exceed the heavy metals limits given in the individual monographs in terms of micrograms of lead per gram of the test substance.

The test consists of three consecutive operations: preparation of the test solutions (procedures 1 to 5), development of the coloured precipitate by reaction with thioacetamide, and comparison of the colours thus obtained either by directly comparing the coloration of liquids in suitable comparison tubes (Method A) or by comparing the intensity of coloured residues obtained by filtering the liquid using an appropriate apparatus (Methods B or C). Method A is generally applicable only when the amount of heavy metals in the weight of the test substance used exceeds 5 µg; Methods B or C can also be used for amounts of 2 to 5 µg of heavy metals.

## PREPARATION OF THE TEST SOLUTIONS

For the standard solution, unless otherwise specified, dilute lead PbTS containing 10 µg of lead per mL solvent to obtain a solution containing 1 µg of lead per mL or 2 µg of lead per mL, depending on the limit prescribed in the monograph. Use the solvent used to prepare the sample solution.

*Procedure 1.* For the sample solution, unless otherwise specified in the monograph, weigh the quantity of the substance to be examined and dissolve it in 25 mL of water R. For the reference solution, add 2 mL of the sample solution to 10 mL of the standard solution. For the blank solution, add 2 mL of the sample solution to 10 mL of water R.

*Procedure 2.* For the sample solution, unless otherwise specified in the monograph, weigh the quantity of the substance to be examined and dissolve it in about 25 mL of the organic solvent specified in the monograph, containing a minimum percentage of water R (for example, dioxan R containing 15% of water R or acetone R containing 15% of water R). For the reference solution, add 2 mL of the sample solution to 10 mL of the standard solution. For the blank solution, add 2 mL of the sample solution to 10 mL of the solvent used to prepare the sample solution.

*Procedure 3.* For the sample solution, place the prescribed quantity (not more than 2 g) of the substance to be examined in a silica crucible with 4 mL of a 250 g/L solution of magnesium sulfate R in sulfuric acid (~98 g/L) TS. Mix using a fine glass rod. Heat cautiously. If the mixture is liquid, evaporate gently to dryness on a water bath. Progressively heat to ignition and continue heating until an almost white or, at most, greyish residue is obtained. Carry out the ignition at a temperature not exceeding 800 °C. Allow to cool. Moisten the residue with a few drops of sulfuric acid (~98 g/L) TS. Evaporate, ignite again and allow to cool. The total period of ignition must not exceed two hours. Take up the residue in two quantities, each of 5 mL, of hydrochloric acid (~70 g/L) TS. Add 0.1 mL of diluted phenolphthalein/ethanol TS, then ammonia (~35 g/L) TS, until a pink colour is obtained. Cool, add anhydrous acetic acid R until the solution is decolorized and add 0.5 mL in excess. Filter if necessary and wash the filter. Dilute with water R to 20 mL.

For the reference solution, follow the procedure described for the sample solution, using the prescribed volume of dilute lead PbTS containing 10 µg of lead per mL instead of the substance to be examined. To 10 mL of the solution obtained, add 2 mL of the sample solution.

For the monitor solution, follow the procedure described for the sample solution, adding to the substance to be examined the volume of dilute lead PbTS prescribed for the preparation of the reference solution. To 10 mL of the solution obtained add 2 mL of the sample solution.

For the blank solution, add 2 mL of the sample solution to 10 mL of water R.

*Procedure 4.* For the sample solution, unless otherwise specified in the monograph, mix thoroughly in a silica crucible the prescribed quantity of the substance to be examined with 0.5 g of magnesium oxide R1. Ignite to a dull redness until a homogeneous white or greyish-white mass is obtained. If after 30 minutes of ignition the mixture remains coloured, allow to cool, mix using a fine glass rod and repeat the ignition. If necessary, repeat the operation. Heat at 800 °C for about one hour. Take up the residue in two quantities, each of 5 mL, of a mixture of equal volumes of hydrochloric acid (~250 g/L) TS and water R. Add 0.1 mL of diluted phenolphthalein/ethanol TS and then ammonia (~35 g/L) TS until a pink colour is obtained. Cool, add anhydrous acetic acid R until the solution is decolorised, then add 0.5 mL in excess. Filter if necessary and wash the filter. Dilute with water R to 20 mL.

For the reference solution, follow the procedure described for the sample solution, using the prescribed volume of dilute lead PbTS containing 10 µg of lead per mL instead of the substance to be examined and drying in an oven at 100 °C to 105 °C. To 10 mL of the solution obtained, add 2 mL of the sample solution.

For the monitor solution, follow the procedure described for the sample solution, adding to the substance to be examined the volume of dilute lead PbTS prescribed for the preparation of the reference solution and drying in an oven at 100 °C to 105 °C. To 10 mL of the solution obtained add 2 mL of the sample solution.

For the blank solution, add 2 mL of the sample solution to 10 mL of water R.

**Procedure 5.** For the sample solution, unless otherwise specified in the monograph, place the prescribed amount of the substance to be examined (not more than 0.5 g) in a suitable, clean beaker. Add successively 2.7 mL of cadmium-free and lead-free sulfuric acid (~1760 g/L) TS, 3.3 mL of cadmium-free and lead-free nitric acid (~1000 g/L) TS, and 2.0 mL of hydrogen peroxide (~330 g/L) TS using a magnetic stirrer. Allow the substance to react with the reagent before adding the next one. Transfer the mixture to a dry high-pressure digestion vessels (fluoropolymer or quartz glass).

For the reference solution, follow the procedure described for the sample solution, using the prescribed volume of dilute lead PbTS containing 10 µg of lead per mL instead of the substance to be examined.

For the monitor solution, follow the procedure described for the sample solution, adding to the substance to be examined the volume of dilute lead PbTS prescribed for the preparation of the reference solution.

For the blank solution, prepare the solution as described for the sample solution, omitting the substance to be examined.

**CAUTION.** When using high-pressure digestion vessels, the safety precautions and operating instructions given by the manufacturer must be followed. The digestion cycles have to be elaborated depending on the type of microwave oven to be used (for example, energy-controlled microwave ovens, temperature-controlled microwave ovens or high-pressure ovens). The cycle must conform to the manufacturer's instructions. The digestion cycle is suitable if a clear solution is obtained.

Close the vessels and place them in a laboratory microwave oven. Digest using a sequence of two separate suitable programmes. Design the programmes in several steps in order to control the reaction, monitoring pressure, temperature or energy depending on the type of microwave oven available. After the first programme, allow the digestion vessels to cool before opening.

Add to each vessel 2.0 mL of hydrogen peroxide (~330 g/L) TS and digest using the second programme. After the second programme, allow the digestion vessels to cool before opening. If necessary to obtain a clear solution, repeat the addition of hydrogen peroxide (~330 g/L) TS and the second digestion programme.

Cool, dilute cautiously with water R and rinse into a flask, ensuring that the total volume does not exceed 25 mL.

### Colour development and measurement

*For Procedures 1 to 4*

**Method A.** Use matched flat-bottomed comparison tubes of transparent glass with a uniform internal diameter of 16 mm for the comparison of the colours. "Matched tubes" means tubes that are matched as closely as possible in internal diameter and in all other respects.

Transfer 12 ml of each of the test solutions prepared as described under *Preparations of the test solutions* to comparison tubes, add 2 mL of acetate buffer, pH 3.5, TS and mix. Add 1.2 mL of freshly prepared thioacetamide reagent TS, mix and allow to stand for two minutes.

Compare the colours of the solutions by viewing down the vertical axis of the tube in diffused light against a white or, if necessary, a black background, or by another suitable method. The test is not valid unless the colour of the reference solution is more intense than the colour of the blank solution. If the use of a monitor solution is prescribed, the colour of the monitor solution is at least as intense as the colour of the reference solution.

The sample complies with the requirements of the test when the colour of the test solution is not darker than the reference solution.

**Method B.** Transfer 12 ml of each of the test solutions prepared as described under *Preparations of the test solutions* to a beaker, add 2 mL of acetate buffer, pH 3.5, TS and mix. Add 1.2 mL of freshly prepared thioacetamide reagent TS, mix and allow to stand for two minutes.

Filter the solutions through a suitable membrane filter (nominal pore size 0.45 µm). Carry out the filtration slowly and uniformly, applying moderate and constant pressure to the piston.

Compare the intensity of the coloration of the residues obtained with the different test solutions on the membrane filters. The test is not valid unless the coloured residue obtained with the reference solution is more intense than the coloured residue obtained with the blank solution. If the use of a monitor solution is prescribed, the coloured residue obtained with the monitor solution is at least as intense as the coloured residue obtained with the reference solution.

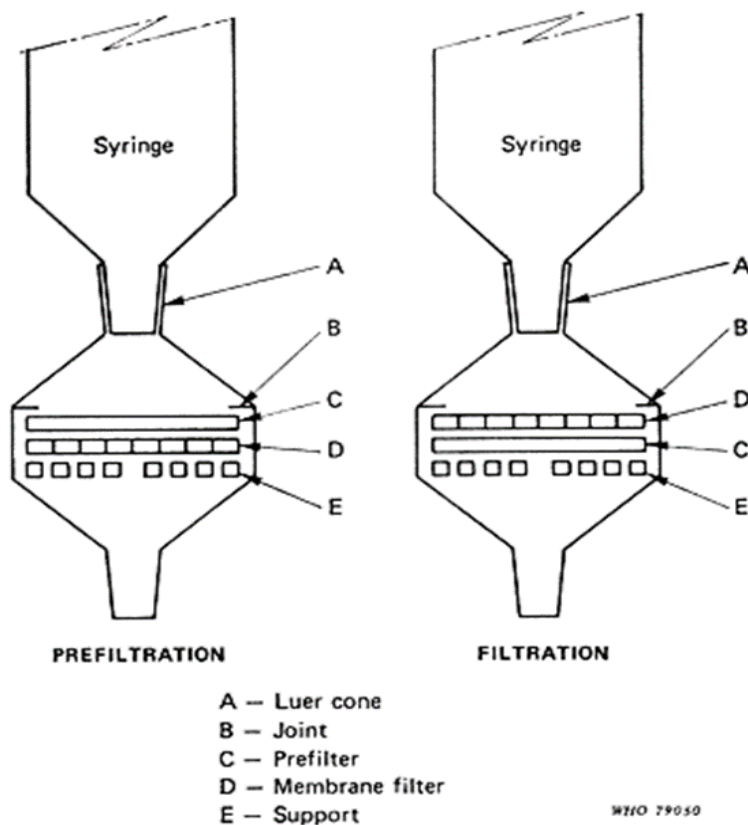
The sample complies with the requirements of the test when the coloured residue obtained from the test solution is not more intense than the coloured residue from the lead standard.

*For Procedure 5:*

**Method C.** Using short-range pH indicator paper, adjust the test solutions to pH 3.0–4.0 with ammonia (~260 g/L) TS. (Ammonia (~100 g/L) TS may be used as the specified range is approached). To avoid heating of the solutions, use an ice bath and a magnetic stirrer. Dilute to 40 mL with water R and mix. Add 2 mL of acetate buffer, pH 3.5, TS and mix. Add to 1.2 mL of thioacetamide reagent R. Mix immediately. Dilute to 50 mL with water R, mix and allow to stand for two minutes. Filter the solutions through a suitable membrane filter (nominal pore size 0.45 µm). Carry out the filtration slowly and uniformly, applying moderate and constant pressure to the piston.

Compare the spots on the filters obtained with the different solutions. The test is not valid unless the coloured residue obtained with the reference solution is more intense than the coloured residue obtained with the blank solution. The coloured residue obtained with the monitor solution is at least as intense as the coloured residue obtained with the reference solution.

The sample complies with the requirements of the test when the coloured residue obtained with the sample solution is not more intense than the coloured residue obtained with the reference solution.



#### REAGENTS TO BE ADDED OR REVISED

##### Acetate buffer, pH 3.5, TS

**Procedure.** Dissolve 25.0 g of ammonium acetate R in 25 mL of water R and add 38.0 mL of hydrochloric acid (~250 g/l) TS. Adjust the pH, if necessary, with hydrochloric acid (~70 g/L) TS or ammonia (~100 g/L) TS. Dilute with water R to 100.0 mL.

##### Magnesium oxide R1

Complies with the requirements prescribed for magnesium oxide R with the following modifications:

Arsenic: maximum 2 ppm.

Heavy metals (2.2.3): maximum 10 ppm.

Iron: maximum 50 ppm.

**Phenolphthalein/ethanol TS, diluted**

*Procedure.* Dissolve 0.1 g of phenolphthalein R in sufficient ethanol (~750 g/L) TS to produce 100 mL.

*Sensitivity test.* To 0.1 mL of the phenolphthalein solution add 100 mL of carbon dioxide-free water R. The solution is colourless. Not more than 0.2 mL of 0.02 M sodium hydroxide is required to change the colour to pink. Colour change: pH 8.2 (colourless) to pH 10.0 (red).

**Thioacetamide R**

$C_2H_5NS = 75.13$  (62-55-5).

General reagent grade of commerce.

White crystals or crystalline powder; melting point, about 113 °C.

**Thioacetamide reagent TS**

Add 1 mL of a mixture of 15 mL of 1M sodium hydroxide, 5 mL of water and 20 mL of glycerol (85%) to 0.2 mL of thioacetamide solution, heat in a water bath for 20 seconds, cool and use immediately.

**Thioacetamide solution TS**

A 4% w/v solution of thioacetamide R.

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**Draft Guidelines****Guidelines on Validation – Appendix 4  
Analytical Method Validation**

**This is a draft proposal of a revision for *Guidelines on Validation, Appendix 4– Analytical Method Validation (Working document QAS/16.671/Rev.1)*. The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).**

**BACKGROUND INFORMATION**

The need for revision of the published *Supplementary guidelines on good manufacturing practices: validation (1)* was identified by the Prequalification of Medicines Programme and a draft document was circulated for comments in early 2013. The focus of the revision was the Appendix on non-sterile process validation (Appendix 7) which had been revised and was adopted by the Expert Committee at its forty-ninth meeting in October 2014.

The main text was sent out for consultation as a *Working document QAS/15.639* entitled “*Guidelines on Validation*” which constituted the general principles of the new guidance on validation.

The draft on the specific topics, the appendices to this main text, will follow. One of them, **Analytical method validation**, constitutes this working document.

The following is an overview on the appendices that are intended to complement the general text on validation:

**Appendix 1**

*Validation of heating, ventilation and air-conditioning systems (HVAC)*

→ will be replaced by cross-reference to the World Health Organization (WHO) Guidelines on GMP for HVAC systems for considerations in qualification of HVAC systems (Annex 8 in TRS 1010, 2018).

**Appendix 2**

*Validation of water systems for pharmaceutical use*

→ will be replaced by cross-reference to the *WHO Guidelines on water for pharmaceutical use for consideration in qualification of water purification systems*.

**Appendix 3**

*Cleaning validation* – consensus to retain.

**Appendix 4**

***Analytical method validation* – updated text proposed in this working document.**

**Appendix 5**

*Validation of computerized systems* – (update – see working document QAS/16.667).

**Appendix 6**

*Qualification of systems and equipment* – update in process.

**Appendix 7**

*Non-sterile process validation* – update already published as Annex 3, WHO Technical Report Series, No. 992, 2015.

## **APPENDIX 4**

### **ANALYTICAL METHOD VALIDATION**

1. Principle
2. General
3. Pharmacopoeial methods
4. Non-pharmacopoeial methods
5. Method validation
6. Method verification
7. Method transfer
8. Revalidation
9. Characteristics of analytical procedures

#### **1. PRINCIPLE**

1.1 This appendix presents some information on the characteristics that should be considered during validation of analytical methods. Approaches other than those specified in this appendix may be followed and may be acceptable. Manufacturers should choose the validation protocol and procedures most suitable for testing of their product.

1.2 The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose.

1.3 Analytical methods, whether or not they indicate stability, should be validated.

1.4 The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.

1.5 The recommendations as provided for in good laboratory practices and guidelines for transfer of technology should be considered, where applicable, when analytical method validation is organized and planned.

#### **2. GENERAL**

2.1 There should be specifications for both materials and products. The tests to be performed should be described in the documentation on standard test methods.

2.2 Specifications and standard test methods in pharmacopoeias ("pharmacopoeial methods"), or suitably developed specifications or test methods ("non-pharmacopoeial methods") as approved by the national regulatory authority (NRA) may be used.

2.3 Well-characterized reference materials, with documented purity, should be used in analysis.

2.4 The most common analytical procedures include identification tests, assay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing and determination of particle size.

2.5 The results of analytical procedures should be accurate, legible, contemporaneous, original, reliable and reproducible. All results should be archived for an appropriate period of time as defined by the laboratory and be in compliance with NRA requirements.

2.6 The procedure should become part of a continuous verification procedure to demonstrate that it meets the predefined criteria over the life of the procedure.

2.7 Trend analysis and risk assessment should be considered at intervals to ensure that the method is appropriate for its intended application.

2.8 Changes to methods should be managed in accordance with the authorized change control procedure. The variability of reference materials and other factors such as changes in the process for synthesis of the drug substance, changes in the composition of the finished product, changes in the analytical procedure, when analytical methods are transferred from one laboratory to another (when method transfer is not possible), or when major pieces of equipment instruments change should be considered. These should be understood, controlled and, where possible, reduced. Verification or revalidation should be considered where appropriate.

2.9 The scope of verification or degree of revalidation depend on the nature of the change(s) and the outcome of risk assessment.

2.10 There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses ("analyst proficiency").

2.11 The data obtained during method validation and verification should be considered covered by good anything practices (GxP) requirements and are expected to follow the principles of good data and record management practices (2). Their associated metadata are also expected to be retained and subjected to good data and record management practices.

2.12 When computerized systems are used to obtain and process data relating to method validation and verification, they should comply to the principles enunciated in Appendix 5 – Validation of computerized systems.

2.13 Adequate attention should be paid to the method of sample preparation. The description of this step should be as detailed as possible, especially if it can have a significant impact on tests results (for example, particular attention should be paid to details such as sonication time, sonication bath temperature and mixing, and to samples where demixing is known to occur).

2.14 Failures occurring during method validation, and how these were overcome, should be included in the method validation report – it is not acceptable to present only the passing results as it will give a biased image on the reliability of the method and on how it should be applied.

### **3. PHARMACOPOEIAL METHODS**

3.1 When pharmacopoeial methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (verification).

3.2 Pharmacopoeial methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the substance under consideration (no placebo interference).

### **4. NON-PHARMACOPOEIAL METHODS**

4.1 Non-pharmacopoeial methods should be appropriately validated.

### **5. METHOD VALIDATION**

5.1 Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.

5.2 Justification should be provided when non-pharmacopoeial methods are used if pharmacopoeial methods are available. Justification should include data such as comparisons with the pharmacopoeial or other methods.

5.3 Standard test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, reference standards, the formulae for the calculation of results and system suitability tests.

### **6. METHOD VERIFICATION**

6.1 Method verification consists of partial validation. It should be performed for already validated analytical methods under the following circumstances:

(a) when an already validated method is used on a product for the first time (for example, in case of a change in active pharmaceutical ingredient (API) supplier, change in the method of synthesis or after reformulation of a drug product); and

(b) when an already validated method is used for the first time in a laboratory (in some cases, method transfer may be preferable).



6.2 Method verification may include only the validation characteristics of relevance to the particular change. For instance, in the case of a change in API supplier, the only expected difference would be in the impurity profile or solubility of the API, and therefore, for a related substances method, there should be an appropriate verification that the method is able to detect and quantitate all potential impurities, even the late eluting ones. Specificity should be among the tests considered (see sections 9 and 10 below for more detail).

6.3 Method verification is suitable in lieu of method validation for pharmacopoeial methods.

## 7. METHOD REVALIDATION

7.1 Methods should be maintained in a validated state over the life of the method (see point 2.6 above). Revalidation of an analytical procedure should be considered whenever there are changes made to the method, including:

- changes to the mobile phase (please refer to *The International Pharmacopoeia* and other pharmacopoeias for the acceptance limits beyond which revalidation must be performed);
- changes to the column;
- changes to the temperature of the column;
- changes to the concentration/composition of the sample and standards; and
- changes to the detector (change in detector type, for example, if going from ultraviolet (UV)-visible detection to fluorimetry, or wavelength of detection).

7.2 In case of repeated system suitability failures or when obtaining of doubtful results. In such cases, an investigation of the root cause should be performed, the appropriate changes made and the method revalidated.

7.3 Periodic revalidation of analytical methods should be considered according to a period that is scientifically justifiable.

7.4 It is acceptable for revalidation to include only the validation characteristics of relevance to the particular change and method.

## 8. METHOD TRANSFER

8.1 During method transfer, documented evidence should be established to prove that a method has equivalent performance when used in a laboratory different from that where it has been originally validated.

8.2 Generally, it should be performed by comparing a set of results obtained by an analyst in one laboratory to that obtained by another analyst at the laboratory to which the method is being transferred.

8.3 The two sets of results should be statistically compared and the differences between the two sets of test results should be within an acceptable range.

8.4 Method transfer should be performed before the testing of samples with a view to obtaining critical data for a dossier, such as process validation or stability studies or applied for routine use.

8.5 A predefined protocol should be followed which includes at least: a title, objective, scope, responsibilities of the sending unit (SU) and the receiving unit (RU); a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any); procedure for the handling of deviations; references; and details of reference samples (starting materials, intermediates and finished products). The protocol should be authorized and dated.

8.6 In the case of independent testing by a separate entity, such as a national quality control testing laboratory that is testing samples on its market, method transfer is not always possible. It is not considered an obligation but may be considered as an optional step when encountering difficulties in applying any particular method. See *WHO guidelines on transfer of technology in pharmaceutical technology* (3) for further reference.

## 9. CHARACTERISTICS OF ANALYTICAL PROCEDURES

9.1 Characteristics that should be considered during validation of analytical methods include:

- specificity;
- linearity;
- range;
- accuracy;
- precision;
- detection limit;
- quantitation limit; and
- robustness.

This list should be considered typical but occasional exceptions should be dealt with on a case-by-case basis

9.1.1 *Accuracy* is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure, for example, three concentrations/three replicates each.

*Note:* It is acceptable to use a “spiked” placebo where a known quantity or concentration of a reference material is used.

9.1.2 *Precision* is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping) and expressed as the relative standard deviation (RSD).

9.1.2.1 *Repeatability* should be assessed using a minimum of nine determinations covering the specified range for the procedure, for example, three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

9.1.2.2 *Intermediate precision* expresses within-laboratory variations (usually on different days, different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.

9.1.2.3 *Reproducibility* expresses *precision* between laboratories.

9.1.3 *Robustness* is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase and should show the reliability of an analysis when deliberate variations are made in method parameters.

9.1.3.1 Factors that can have an effect on robustness when performing chromatographic analysis include:

- verification of stability of test and standard samples and solutions;
- reagents (for example, different suppliers);
- different columns (for example, different lots and/or suppliers);
- variation of extraction time;
- variations of pH;
- variations in mobile phase composition;
- temperature; and
- flow rate.

The variation of extraction time and the verification of stability of analytical solutions are of particular importance

9.1.4 *Linearity* indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used. If linearity is not attainable, a nonlinear model may be used.

9.1.5 *Range* is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable for the product. The specified range is normally derived from linearity studies.

9.1.6 *Specificity (selectivity)* is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation.

9.1.7 *Detection limit (limit of detection)* is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:

- visual evaluation;
- signal to noise ratio;
- standard deviation of the response and the slope;
- standard deviation of the blank; and
- calibration curve.

9.1.8 *Quantitation limit (limit of quantitation)* is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:

- signal to noise ratio;
- standard deviation of the response and the slope;
- standard deviation of the blank; and
- calibration curve.

9.2 Characteristics (including tests) that should be considered when using different types of analytical procedures are summarized in Table 1:

Table1. Characteristics to consider during analytical validation

Type of analytical procedure	Identification	Testing for impurities	Testing for impurities	Assay — dissolution (measurement only) — content/potency
Characteristics		Quantitative tests	Limit tests	
Accuracy	–	+	–	+
<i>Precision</i>				
Repeatability	–	+	–	+
Intermediate precision <sup>a</sup>	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	– <sup>b</sup>	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated;

+ Characteristic should normally be evaluated.

<sup>a</sup> In cases where a reproducibility study has been performed, intermediate precision is not needed.

<sup>b</sup> May be needed in some cases.

Statistical analysis used to evaluate validation characteristics against predetermined acceptance criteria should be appropriate for the intended evaluation. Appropriately validated software should be used. An appropriate number of samples to provide adequate statistical power and range should be considered.

### 9.3 System suitability testing

**Note:** System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analysed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure being evaluated, for instance, a resolution test for a high-performance liquid chromatography (HPLC) procedure.

9.3.1 The suitability of the entire system should be confirmed prior to and during method validation tests as well as during the test of samples.

9.3.2 System suitability runs should include only reference materials or established standards of known concentration to provide an appropriate comparator for the potential variability of the instrument. The sample material or product under test should not be used as a standard to evaluate suitability of the system (see *General guidelines for the establishment, maintenance and distribution of chemical reference substances*).

### References

1. *Supplementary guidelines on good manufacturing practices: validation* (WHO Technical Report Series, No. 937, 2006, Annex 4).
2. *General guidelines for the establishment, maintenance and distribution of chemical reference substances* WHO *Guidelines on good data and record management practices* (WHO Technical Report Series, No. 943, 2007, Annex 3).
3. *WHO guidelines on transfer of technology in pharmaceutical technology* (WHO Technical Report Series, No. 961, 2011, Annex 7).

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## Guidelines on Validation – Appendix 6 Qualification

**This is a draft proposal of a revision for *Guidelines on Validation, Appendix 6 - Qualification* (Working document QAS/16.673/Rev.2). The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).**

### BACKGROUND INFORMATION

The need for revision of the published *Supplementary guidelines on good manufacturing practices: validation* (World Health Organization (WHO) Technical Report Series, No. 937, 2006, Annex 4) was identified by the Prequalification of Medicines Programme and a draft document was circulated for comments in early 2013. The focus of the revision was the Appendix on non-sterile process validation (Appendix 7), which had been revised and was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) at its forty-ninth meeting in October 2014.

The main text was sent out for consultation as a *working document* QAS/15.639 entitled *Guidelines on validation* which constitute the general principles of the new guidance on validation.

The draft on the specific topics, the appendices to this main text, will follow. One of them, the *Validation on qualification of systems, utilities and equipment*, newly entitled *Guidelines on qualification*, constitutes this working document.

The following is an overview on the appendices that are intended to complement the general text on validation:

#### Appendix 1

*Validation of heating, ventilation and air-conditioning systems (HVAC)*

→ will be replaced by cross-reference to the WHO Guidelines on GMP for HVAC systems for considerations in qualification of HVAC systems  
(– Annex 8 in TRS 1010, 2018)

#### Appendix 2

*Validation of water systems for pharmaceutical use*

→ will be replaced by cross-reference to *WHO Guidelines on water for pharmaceutical use for consideration in qualification of water purification systems*

#### Appendix 3

*Cleaning validation* – consensus to retain

#### Appendix 4

*Analytical method validation*

→ will be replaced by update – working document QAS/16.671

#### Appendix 5

*Validation of computerized systems*

→ will be replaced by update – working document QAS/16.667

#### Appendix 6

*Guideline on Qualification – updated text proposed in this working document*  
(new title)

#### Appendix 7

*Non-sterile process validation – update already published as Annex 3, WHO Technical Report Series, No. 992, 2015*

**Brief background on the changes in this document**

There was some confusion regarding the title. It is therefore suggested to change the title to GUIDELINES ON QUALIFICATION. In this way, the general principles in qualification are addressed which can be applied for systems, equipment, and so on.

Based on the comments, the general chapters on objective and scope were written to make it clear that the guidelines address principles of qualification that can be applied, as appropriate, to premises, systems, utilities and equipment and to include the application of risk management principles.

Moreover, duplication was removed, logical flow of concepts addressed and aligned with international texts and the comments. The V Model has been removed based on the feedback received. In the former published text on qualification, protocol formats were included. These protocol formats were extracted from training materials and were intended to serve as examples.

In view of the feedback that seemingly manufacturers took them as absolute examples to be used, these examples have been removed in the current version.

**APPENDIX 6  
GUIDELINES ON QUALIFICATION**

1. Principle
2. Scope
3. Glossary
4. General
5. User requirement specifications
6. Design qualification
7. Factory acceptance test and site acceptance test
8. Installation qualification
9. Operational qualification
10. Performance qualification
11. Periodic review and requalification

**1. PRINCIPLE**

- 1.1 In principle, premises, systems, utilities and equipment should be appropriately designed, installed, qualified, operated, cleaned and maintained to suit their intended purpose.
- 1.2 Quality management systems should be in place to ensure that these remain in a qualified state throughout their life cycle.
- 1.3 Products should be manufactured on qualified equipment.
- 1.4 Manufacturers who may use an alternative verification framework to achieve qualification should ensure the qualification expectations within this guide are satisfied.

**2. SCOPE**

- 2.1 These guidelines describe the general approach to qualification, for example, premises, systems, computerized system, utilities and equipment.
- 2.2 The principles in these guidelines may also be applied to the qualification of instruments, analytical instruments and testing devices, where appropriate.
- 2.3 These may include and are not limited to: certain rooms; water purification systems; cleaning systems; heating, ventilation and air conditioning systems; compressed air systems; gas systems; steam systems; as well as production equipment and analytical instruments.

2.4 Separate guidelines in this series address other principles in validation such as process validation and cleaning validation (see references at the end of this document).

2.5 The principle can be used when de-commissioning equipment to show that it remains fit for its purpose throughout the life cycle.

### 3. GLOSSARY

**computerized system.** A computerized system collectively controls the performance and execution of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, for example, manuals and standard operating procedures (SOPs), as well as personnel interacting with hardware and software.

**design qualification.** Documented evidence that, for example, the premises, supporting systems, utilities and equipment have been designed for their intended purposes and in accordance with the requirements of good manufacturing practices (GMP).

**factory acceptance test.** A test conducted, usually at the vendor's premises, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications. (*new*)

**installation qualification.** The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

**operational qualification.** Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

**performance qualification.** Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods. (In the context of systems, the term "process validation" may also be used.)

**site acceptance test.** A test conducted at the site of use to verify that the system, equipment or utility, as assembled or partially assembled meets approved specifications. (*new*)

**system.** A regulated pattern of interacting activities and techniques that are united to form an organized whole.

**user requirement specifications.** An authorized document that defines the requirements for use of the system, equipment or utility in its intended production environment. (*amended*)

**utility.** A system consisting of one or more components to form a structure designed to collectively operate, function or perform and provide a service such as electricity, water, ventilation or other. (*new*)

### 4. GENERAL

*Note: The remainder of the text in these guidelines will refer to utilities and equipment as examples, even though the principles may be applicable to others such as premises and systems.*

4.1 The validation master plan, or other relevant document, should specify the policy, organization, planning, scope and stages applied in qualification on site, and should cover, for example, production, quality control and engineering.

4.2 Quality risk management principles should be applied in qualification. These include:

- A clear understanding of the system, and the role it plays in establishing/protecting the process and quality and all of the potential ways (risks) the process or quality could be impacted by failures, events, errors, or time/use-based factors (deterioration, out of tolerance instruments, wear and tear, and so on);
- Defining all of the Design, Procedural and/or Quality System Controls required to protect against these potential risks. These controls either mitigate/reduce the risks and/or detect the impact to quality or process – should the risk occur. (To ensure the "failure" does not impact final product quality);
- Compiling evidence during the design, engineering, commissioning and qualification to demonstrate that all of these required "controls" have been properly implemented and verified. (Including "function" where applicable – such as alarms on operating parameters);
- Appropriate control and oversight of change once the controls have been verified.

4.3 The scope and extent of qualification and requalification should be determined based on the principles of impact assessment and risk management principles.

4.4 Qualification should be executed by trained personnel. Training records should be maintained.

4.5 Where appropriate, new premises, systems, utilities and equipment should be subjected to all stages of qualification. This includes the preparation of user requirement specifications (URS), design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

4.6 Justification should be provided where it is decided that not all stages of qualification are required.

4.7 Qualification should be done in accordance with predetermined and approved qualification protocols. The protocol should specify the prerequisites and test details, including acceptance criteria.

4.8 The results of the qualification should be recorded and reflected in qualification reports.

4.9 A qualification report prepared at the completion of each protocol or stage of qualification (Installation/Operational/Performance) should include, or reference as appropriate, the following:

- test results, including supporting calculations, documentation and raw/original data,
- test failures,
- protocol departures,
- recommendations and justification for issue resolution, and
- conclusions.

4.10 There should be a logical sequence for executing qualification, such as premises (rooms), then utilities and equipment.

4.11 Normally, qualification stages should be sequential. (For example, operational qualification should follow after the successful completion of installation qualification.) In some cases, different stages of qualification may be executed concurrently. This should be justified and documented in the validation master plan (or qualification protocol).

4.12 Equipment should be released for routine use only once there is documented evidence that the qualification has been successful.

4.13 Certain stages of the qualification may be done by a supplier or a third party, subject to the conditions and responsibilities as defined in a written agreement between the parties. The contract giver remains responsible to ensure that the qualification is done in accordance with the principles of GMP.

4.14 The relevant documentation associated with qualification, including SOPs, specifications and acceptance criteria, certificates and manuals, should be available.

4.15 Utilities and equipment should be maintained in a qualified state and should be periodically reviewed for the need for requalification. Requalification should be considered when changes are made.

## **5. USER REQUIREMENT SPECIFICATIONS**

5.1 URS should be prepared for, but not limited to, utilities and equipment, as appropriate.

5.2 URS should be used at later stages in qualification to verify that the purchased and supplied utility or equipment is in accordance with the user's needs.

## **6. DESIGN QUALIFICATION**

6.1 DQ should demonstrate that the system, as designed, is appropriate for its intended use as defined in the URS.

6.2 A suitable supplier should be selected and approved for the relevant utility or equipment.



## **7. FACTORY ACCEPTANCE TEST AND SITE ACCEPTANCE TEST**

7.1 Where a utility or equipment is assembled, or partially assembled at a site other than that of the purchaser or end-user, testing and verification may be done, based on quality risk management principles, to ensure that it is appropriate and ready for dispatch.

7.2 The checks and tests during factory acceptance test (FAT) should be recorded.

7.3 The acceptability of the assembly and overall status of the utility or equipment should be described in a conclusion of the report for the FAT, prior to shipment.

7.4 Tests, based on quality risk management principles, may be performed to verify the acceptability of the utility or equipment when it is received at the end-user. This is a site acceptance test (SAT).

7.5 The results of the tests should be evaluated and the outcome of the acceptability of the utility or equipment should be recorded in the conclusion section of the report for the SAT.

## **8. INSTALLATION QUALIFICATION**

8.1 Utilities and equipment should be correctly installed, in an appropriate location.

8.2 There should be documented evidence of the installation. This should be in accordance with the IQ protocol which contains all the relevant details.

8.3 IQ should include identification and installation verification of relevant components identified, e.g. services, controls and gauges.

8.4 Identified measuring, control and indicating devices, should be calibrated on site unless otherwise appropriately justified. The calibration should be traceable to national or international standards. Traceable certificates should be available.

8.5 Deviations and non-conformances, including those from URS, DQ and acceptance criteria specified and observed during installation, should be recorded, investigated, and corrected or justified.

8.6 Normally, the outcome of the IQ should be recorded in the conclusion of the report, before OQ is started.

## **9. OPERATIONAL QUALIFICATION**

9.1 Requirements and procedures for operation (or use), calibration, maintenance and cleaning should normally be prepared normally before OQ and approved prior to PQ.

9.2 Utilities and equipment should operate correctly and their operation should be verified in accordance with an OQ protocol. OQ normally follows IQ but, depending on the complexity of utility or equipment, it may be performed as a combined installation/operation qualification (IOQ). This should be justified and documented in the validation master plan (or qualification protocol).

9.3 OQ should include, but is not limited to, the following:

- tests that have been developed from the knowledge of processes, systems and equipment to ensure the utility or equipment is operating as designed; and
- tests to confirm upper and lower operating limits, and/or "worst case" conditions.

9.4 Training of operators for the utilities and equipment should be provided and training records maintained.

9.5 Calibration, cleaning, maintenance, training and related tests and results should be verified to be acceptable.

9.6 Deviations and non-conformances observed should be recorded, investigated and corrected or justified.

9.7 The results for the verification of operation should be documented in the OQ report.

The outcome of the OQ should be recorded in the conclusion of the report, normally before PQ is started.

## 10. PERFORMANCE QUALIFICATION

10.1 PQ should normally follow the successful completion of IQ and OQ. In some cases, it may be appropriate to perform PQ in conjunction with OQ or process validation. This should be justified and documented in the validation master plan (or qualification protocol).

10.2 PQ should include, but is not limited to, the following:

- tests using production materials, qualified substitutes or simulated products proven to have equivalent behaviour under normal operating conditions with worst case scenario and batch sizes where appropriate; and
- tests should cover the intended operating range.

10.3 Utilities and equipment should consistently perform in accordance with their design specifications and URS. The performance should be verified in accordance with a PQ protocol.

10.4 There should be records (for example, a PQ report) for the PQ to indicate the satisfactory performance over a predefined period of time. Manufacturers should justify the period over which PQ is done.

## 11. PERIODIC REVIEW AND REQUALIFICATION

11.1 Utilities and equipment should be maintained in a qualified state through the life cycle of the utility or equipment.

11.2 Utilities and equipment should be reviewed periodically to confirm that they remain in a qualified state or to determine the need for requalification.

11.3 Where the need for requalification is identified, this should be performed.

11.4 Risk management principles should be applied in the review and requalification and the possible impact of small changes over a period of time should further be considered (such as, through change control).

11.5 Risk management principles may include factors such as calibration, verification, maintenance data and other information.

11.6 The qualification status and requalification due dates should be documented, for example, in a qualification matrix, schedule or plan.

11.7 In case a utility or equipment in use is identified, where it had not been subjected to qualification, a qualification protocol should be prepared where elements of URS, design specifications, operation and performance are verified for acceptability. The outcome of this qualification should be recorded in a report.

### Reference documents for additional reading

*[Note from the Secretariat: The references below will be updated upon finalization of the related texts.]*

See WHO TRS 970, 2012, Annex 2, for aspects to be considered for inclusion in qualification of water purification systems.

See WHO TRS 1010, 2018, Annex 8, for aspects to be considered for inclusion in qualification of heating, ventilation and air-conditioning (HVAC) systems.

See WHO TRS XXX for aspects to be considered for inclusion in qualification and validation of computerized systems (QAS working document QAS/16.667).

See WHO TRS 992, 2015, Annex 3, for aspects to be considered in process validation.

See WHO TRS XXX for aspects to be considered in analytical method validation (QAS working document QAS/16.671)

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