LABELLING REVIEW FOR PREQUALIFICATION ASSESSMENT

Prequalification of In Vitro Diagnostics

Contents

1. Introduction

World Health Organization (WHO) prequalification of in vitro diagnostics (IVDs) is coordinated through the department of Regulation and Prequalification. Focus is placed on IVDs for priority diseases and their suitability for use in resource-limited settings.

WHO prequalification of IVDs is a comprehensive quality assessment of individual IVDs through a standardized procedure aimed at determining whether the product meets WHO prequalification requirements.

The prequalification assessment process includes the following components:

- review of a product dossier;
- performance evaluation including operational characteristics;
- manufacturing site(s) inspection; and
- labelling review.

Products submitted for prequalification assessment that meet, as determined by WHO, the WHO prequalification requirements are included in the WHO list of prequalified IVDs. The duration of the validity of the prequalification status of a product is dependent on the manufacturer's fulfilment, within the applicable deadlines, of its post-qualification obligations and requirements, including:

- prequalification commitments;
- annual reporting;
- reporting of changes;
- post-market surveillance obligations;
- receiving inspections; and
- ongoing compliance with WHO prequalification technical specifications.

The findings of WHO prequalification are used to assess the safety, quality and performance of commercially available IVDs for the purpose of providing guidance to interested United Nations (UN) agencies and WHO Member States in their procurement decisions.

This document provides information about the labelling review approach for prequalification assessments.

This approach is applied through the initial application for assessment using the pre-submission form and associated documents, product dossier review assessment, manufacturing site(s) inspection, product performance evaluation and final labelling review at the end of the assessment.

This document is intended to be read in conjunction with the *WHO document PQDx_018 Instructions For Compilation Of A Product Dossier – IMDRF ToC* (1) and *Technical Guidance Series 5- Designing instructions for use for in vitro diagnostic medical devices* (2).

2. Intended audience

This document has been prepared to provide prequalification applicants with detailed information about the approach that is used for labelling review at all the stages of prequalification assessment. Scope of the review includes primary and secondary packaging labels, IFU and job aids.

3. Definitions

Labelling	The label, instructions for use, and any other information that is related to identification, technical description, intended purpose and proper use of the IVD medical device, but excluding shipping documents. NOTE 1: Labelling can also be referred to as “information supplied by the manufacturer.” NOTE 2: Labelling can be in printed or electronic format and may either physically accompany the medical device or direct the user to where the labeling information can be accessed (such as through a website).
Label	Written, printed, or graphic information either appearing on the medical device itself, or on the packaging of each unit, or on the packaging of multiple devices
Instructions for use	Instructions for Use: General and technical information provided by the manufacturer to inform the device user of the IVD medical device’s intended purpose and proper use and of any contraindications, warnings, or precautions to be taken. It is provided by the manufacturer to support and assist the device users in its safe and appropriate use. NOTE 1: Instructions for use can also be referred to as “package insert.”
Labelling review	The process of assessing labelling based on the principles of labelling for IVD medical devices to demonstrate the safety and clinical performance of the IVD medical device for its intended use (3).

4. Abbreviations

IMDRF	International Medical Device Regulators Forum is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF) and aims to accelerate international medical device regulatory harmonization and convergence.
IFU	Instructions for use is general and technical information provided by the manufacturer to inform the device user of the IVD medical device's intended purpose and proper use of the IVD medical device.
ISO	International Organization for Standardization is an independent, non-governmental international organization made up of 164 national standards bodies that brings together experts to share knowledge and develop voluntary, consensus-based, market relevant International Standards that support innovation and provide solutions to global challenges.

5. Labelling review approach

The labelling is a critical component of the product. It serves to identify a device and its manufacturer, and to communicate critical information, including on safety, use, and performance. Labelling documents should be developed and evaluated using risk management principles to fulfill prequalification assessment requirements (4).

The purpose of labelling review is to ensure that the content of the label(s), instructions for use (IFU), and information intended for the end-user of the product is sufficient to support the safe and effective use of the IVDs by the intended users and relevant third parties. The labelling review approach is based on WHO PQ guidance, IMDRF guidance (5) and ISO 18113 series concepts, principles and essential requirements (6). For Malaria rapid diagnostic test products, review is also based on Harmonization of rapid diagnostic tests for malaria and implications for procurement (7).

At each stage of the prequalification assessment, labelling is reviewed and the applicant is provided with the respective observations. Once all prequalification assessment components have been completed the applicant is provided with a full set of labelling related observations. Those observations which are identified by WHO as critical must be addressed by the applicant prior to prequalification listing. Non-critical observations are accepted by WHO as prequalification commitments; these shall be addressed by the applicant within the agreed timeframes.

5.1 Pre-submission stage

A completed pre-submission form provides summary information about the product, its regulatory version and manufacturer, and includes labelling and product IFU(s). The pre-submission form (and respective attachments) assists WHO to determine eligibility for prequalification assessment and the type of assessment (full or abridged) that the product will undergo. The IFU review is conducted to have a basic understanding of the operational and performance characteristics, adequacy of the product for use in WHO Member States and in resource-limited settings (i.e. need for cold chain), infrastructure requirements for its use (i.e. electricity) and contents of the kit. Furthermore, IFU is reviewed to determine if it is sufficiently comprehensive to warrant an execution of the laboratory performance evaluation.

5.2 Dossier review stage

WHO reviews the product dossier with the purpose of assessing evidence in support of safety and performance of the product. This is, to verify that the claims made on the IFU are true and have been validated and verified through scientifically sound studies and against international standards where applicable. This part intended to be read in conjunction with the *WHO document PQDx_018 Instructions For Compilation Of A Product Dossier – IMDRF ToC (1).*

5.3 Manufacturing site inspection stage

Labelling is reviewed by the Inspection Team as part of the inspection of the Quality Management System of the manufacturer for clarity, correctness, consistency with the technical documentation, requirements of ISO 13485:2016 standard, and suitability for the target user group in WHO Member States (8). Labelling and IFU components reviewed include *inter alia*:

- Font size for both labelling and IFU;
- Suitability of labelling to hot and humid conditions;
- Universal symbols and warning legibility and comprehensiveness;
- Clarity of diagrams if applicable;
- Document control of IFU and other components/accessories supplied within the kit; and
- Confirmation that IFU procedure is followed during QC testing and final release testing.

5.4 Performance Evaluation

Labelling review is also conducted during performance of an independent laboratory performance evaluation of the IVD to verify that it is comprehensive and clear to the user especially for use in resource-limited settings. The aspects that are reviewed during performance evaluation are ease of use of the product and performance of the product as per IFU. The following components are reviewed:

- Warnings and precautions;
- Materials provided (test device, reagents, calibrators, controls and accessories);
- Materials required but not provided;

- Instrumentation;
- Troubleshooting;
- Collecting and preparing specimens;
- IVD storage, operating conditions and stability;
- Test procedure;
- Reading results; and
- Interpretation of results.
- Limitations of the procedure.

5.5 Final labelling review

The manufacturer submits final labelling for review at the end of the prequalification assessment process, considering requests made during the assessment stages listed above. Review at this time is made to ensure clarity, correctness, consistency with both the information submitted in the product dossier, and with international guidance and requirements, and suitability for the target user group in resource-limited settings. The overall feedback on the labelling review is provided to the manufacturer after final review. If requested by WHO, the manufacturer may amend the labelling before the product can be prequalified or the amendments may be accepted as commitments for prequalification if the manufacturer commits to make the amendments with the next revision of labelling.

5.6 Changes to labelling

A change may introduce new hazards that have not been previously addressed; adversely affect risks associated with existing hazards; and/or alter the presentation of existing or new risks to the user (this can involve labelling changes or new indications for use).

All changes to labelling should be reported to WHO, including those related to actions including field safety corrective actions taken related to concerns arising from post-market surveillance of complaints and adverse events. WHO reviews the proposed changes to labelling in the context of validation and verification or any other relevant evidence in support of the changes to the labelling to ensure that the proposed changes do not affect the safety and clinical performance of the IVD for its intended use (9).

6. References

1. Instructions For Compilation Of A Product Dossier: [Available at https://www.who.int/diagnostics_laboratory/evaluations/200324_draft_Instruction_for_compilation_of_a_product_dossier_pqdx_018_v4_toc.pdf?ua=1.]
2. Technical Guidance Series (TGS) for WHO Prequalification – Diagnostic Assessment-Designing instructions for use for in vitro diagnostic medical device (TGS-5): [Available at: https://apps.who.int/iris/bitstream/handle/10665/259737/WHO-EMP-RHT-PQT-TGS5-2017.05-eng.pdf?sequence=1.]
3. IMDRF/GRRP WG/N52 FINAL:2019: Principles of Labelling for Medical Devices and IVD Medical Devices.
4. Geneva: International Organization for Standardization; 2009. For additional guidance refer to ISO 14971 series Medical devices – Application of risk management to medical devices.
5. http://www.imdrf.org/documents/documents.asp

6. ISO 18113 series. In vitro diagnostic medical IVDs – Information supplied by the manufacturer (labelling) – Part 2: In vitro diagnostic reagents for professional use.
7. Harmonization of rapid diagnostic tests for malaria and implications for procurement. Available at https://www.who.int/malaria/publications/atoz/9789241509978_eng.pdf?ua=1
8. ISO 13485: 2016 Medical devices – Quality management systems – Requirements for regulatory purposes.
9. Reportable Changes to a WHO prequalified in vitro diagnostic medical device (document PQDx_121).
   [Available at: https://apps.who.int/iris/bitstream/handle/10665/251915/WHO-EMP-RHT-PQT-2016.01-eng.pdf;jsessionid=8D3AB2A02EC821B4739472A3995BA699?sequence=1]