Reportable changes to WHO prequalified and emergency use listed in vitro diagnostics

Application guidance

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Document undergoing WHO publishing clearance

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ISBN 978-92-4-010984-1 (electronic version)
ISBN 978-92-4-010985-8 (print version)

Suggested citation. Reportable changes to WHO prequalified and emergency use listed in vitro diagnostics: application guidance. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

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Contents

1 Purpose of this document

This document supersedes "Reportable Changes to a WHO Prequalified In Vitro Diagnostic Medical Device" published in 2016 (also referred to as PQDx_121) which has been revised to include the WHO Emergency Use Listing Procedure (EUL). To introduce a redefined process, integrating a risk-based methodology for reporting changes to WHO. And finally, it aims to align with the latest international best practices, strengthen regulatory reliance and improve process efficiency. The draft of this document was released on 14 October 2024 and posted on https://extranet.who.int/prequal/ for public comment. Public comments were received from IVD Manufacturers, National Regulators and other stakeholders. Based on that draft, this publication was finalized in March 2025.

1.1 Intended audience

This document aims at providing manufacturers with information on the reporting of changes applied to in vitro diagnostic (IVD) products that have been either WHO prequalified or listed as part of the WHO Emergency Use Listing Procedure.

Manufacturers of WHO prequalified or EUL-listed IVDs are required to be aware of and comply with the obligations outlined in this document.

Note: For the purpose of this document the following definition of "manufacturer" applies:

This document does not address the required response to changes made during prequalification/EUL assessment.

For changes implemented during prequalification/EUL assessment process, the manufacturer should contact the PQT-IVD focal points for change requests to seek guidance.

1.2 Scope

This document describes when and how a manufacturer is required to report to WHO a change to a prequalified or EUL listed IVD, including, but not limited to:

- changes to the product design,
- changes related to the manufacturing process(es) and/or site(s) of manufacture,
- changes to the Quality Management System (QMS) that the product was designed and/or manufactured under; and/or
- other reportable "administrative" changes.

This guidance defines what constitutes reportable changes, explains how to assess the impact of such changes, and provides information on the list of required documents based on the determined impact level.

1.3 Background

As part of the life cycle of an IVD, changes to the product, its components, its manufacture (e.g., processes, location), and/or the QMS under which it is produced may become necessary. Reportable changes to prequalified IVD products require prior approval as detailed in this guidance as some of such changes[1] can present little to no potential impact to the quality, safety and/or performance of the IVD or be likely to significantly affect the quality, safety and/or performance of the product.

To enhance the WHO review process for reportable change requests and assist manufacturers with their submissions, WHO has introduced a new system detailed in this guidance. WHO has established criteria for classifying reportable changes into two categories based on their potential impact to the device's quality, performance and safety. Changes with Medium to High potential impact undergo a full review, while those with low potential impact are accepted following the risk categorization check of the application.

Additionally, a comprehensive list of required documents for submission has been established for each category of change impact, ensuring that the process is transparent and equitable for all applicants.

A critical responsibility for manufacturers in this process lies in the evaluation of the potential impact of the proposed change. This document provides detailed guidance on the impact evaluation and Reportable Change Request process enabling manufacturers to align their submissions with WHO's requirements effectively.

1.4 Terms and definitions

1.4.1 **Reportable change:**

- Any change made to the PQ or EUL listed products, to the approved design, and/or to the established quality management system that is demonstrated, through risk analysis, to have a potential impact on the quality, function, performance, usability, safety or the information provided with a prequalified or EUL-listed IVD.

- Any change to the information provided with the product or administrative change that needs to be reflected in the WHO Public Assessment Report (WHOPAR).

For the purposes of this guidance, reportable changes have been classified as "**High/Moderate impact changes" and "Low-impact changes".**

[1] Some regulatory authorities refer to changes as "variations".

A reportable change may introduce new hazards that were not previously addressed, potentially increasing the risks associated with existing hazards. Alternatively, a reportable change may not introduce a new hazard but may require updated mitigation measures to prevent generating new hazards.

1.4.2 **High/Moderate impact change:** A change with the potential to affect the function, quality, performance, usability, and/or safety of an IVD product, associated with risks that have been determined to be high or moderate.

1.4.3 **Low-impact change:** A change with a rationale that demonstrates that has no potential impact or a limited potential impact on the function, quality, performance, usability, and/or safety of an IVD product, associated with risks that have been determined to be low. This includes administrative changes requiring an update to the WHOPAR.

1.4.4 **WHOPAR:** World Health Organization Public Assessment Report, which summarizes the information on the listed products and findings of the prequalification and EUL assessments but excludes confidential and proprietary information.

1.4.5 **WHOPIR:** World Health Organization Public Inspection Report, which summarizes the findings made during the inspection of the manufacturing site(s) as well as corrective actions taken in respect of the site(s) but excludes confidential and proprietary information.

1.4.6 **Non-reportable change:** A change with no potential to affect the function, quality, performance, usability, and/or safety of an IVD product or associated risks. Non-reportable changes are managed only through the manufacturer's QMS and does not need to be reported, according to the provisions outlined in this guidance document. Examples of non-reportable changes are included in this document (see section 3 below).

1.4.7 **Implementation:** For the purpose of this guidance, implementation refers to the release into the market of the changed product, or of products manufactured under changed conditions.

1.4.8 **Manufacturer:** Any natural or legal person with responsibility for design and/or manufacture of a diagnostic product with the intention of making the diagnostic product available for use, under his/her name; whether or not such a diagnostic product is designed and/or manufactured by that person himself/herself or on his/her behalf by another person(s) [1].

2 Maintaining WHO prequalification or eul status of IVDs

The WHO Prequalification Programme or EUL listing is critical in ensuring the quality, safety, and performance of in vitro diagnostic (IVD) products procured for global health programs.

When planning a change impacting a prequalified or EUL listed IVD, the manufacturer must align with its quality assured design change and change control processes. Processes involved must comply with the applicable ISO 13485 standard (or equivalent) [2] and follow a risk assessment process in accordance with ISO 14971 (or equivalent). Further guidance on risk management can be found in the WHO document "TGS 7: Risk management for manufacturers of in vitro diagnostic medical devices". [3]

The management of the change by the manufacturer to maintain WHO Prequalification or EUL status must be well documented and controlled, encompassing risk assessment, planning, review, verification, validation, when applicable, approval, and implementation processes. Documented evidence is essential to ensure data traceability, demonstrate appropriate risk mitigation, and maintain the continued safety, quality, and performance of the IVD.

The manufacturers must notify WHO with any reportable changes prior to their implementation. Therefore, manufacturers must determine and document whether a change is reportable and requires acceptance or approval by the WHO or relevant authorities before implementation (see Figure 1 below).

3 Criteria for determining reportable changes

3.1 Non-reportable changes

Non-reportable changes are changes with no potential to affect the function, quality, performance, usability, and/or safety of an IVD product or associated risks as defined in point 1.4.6 above. Non-reportable changes are managed only through the manufacturer's QMS and don't need to be reported to WHO prior to implementation, provided they do not fall under the definition detailed in the section 3.2 below and are not listed as reportable in Appendix 1.

Examples of non-reportable changes include, but are not limited to, the following:

- Changes to the QMS for maintenance and continuous compliance as set in the manufacturer's quality policy.
- Routine updates of procedures and processes necessary for maintaining ISO 13485 standard or Recognized QMS certifications.
- Introduction of automated systems for QMS or document control or QMS software updates that improve QMS administrative functions but do not affect the product, manufacturing activities, testing, or release of the product itself.
- Change to an already approved alternative supplier or Changes to non-critical suppliers and non-critical components that do not affect product quality, performance, or safety

- Changes to non-critical processes, including those not directly impacting the manufacturing of the IVD.
- Updates of design files or batch records to improve the completeness or clarity of information, without modifying the product's intended use or critical design elements.
- Improvements in post-market surveillance activities or routine updates of controlled QMS procedures with no impact on product quality, performance or safety.

The rationale for determining whether a change is reportable or not must be documented under the manufacturer's QMS and this information can be audited during a routine inspection process by WHO. All change-related activities will remain within the scope of post-prequalification periodic inspections or post-EUL reassessments.

Manufacturers are encouraged to contact WHO when in doubt whether a change should be reported.

3.2 Reportable changes

Reportable changes, as defined in section 3.2 above, are any change made to the PQ or EUL listed products, to the approved design, and/or to the established quality management system that is demonstrated, through risk analysis, to have a potential impact on the quality, function, performance, usability, safety or the information provided with a prequalified or EUL-listed IVD. Any change to the information provided with the product or administrative change that needs to be reflected in the WHO Public Assessment Report (WHOPAR) also falls under the definition of reportable changes (see 5.1.1 below).

These changes must be reported in accordance with the requirements outlined in this guidance to ensure ongoing compliance and transparency regarding the prequalification status.

The following criteria are provided as examples to help determine whether a change is reportable:

- Changes that introduce new risks not previously identified or modify existing risks impacting the quality, safety or performance of the product.
- Changes that modify the probability of existing hazardous situations (re-evaluation) occurring, impacting the quality, safety or performance of the product.
- Changes that require updating or extending the scope of mitigation measures impacting the quality, safety, or performance of the product.
- Change in the nature, quality, attributes or specifications of critical components or reference materials.
- Change in the manufacturing or quality control processes or technologies.
- Changes that alter the presentation to the user or change the information provided to the user (this may involve labelling changes, new indications for use, etc.).
- Changes that modify the information provided with the device (i.e., IFU, quick guide, labels, etc.).
- Administrative changes that require an update of the WHOPAR, this may include an introduction of a new product code or catalogue number, etc.

This is not an exhaustive list.
Changes associated with a prequalified or EUL-listed IVD are exemplified in **Appendix 1,** below,

and considered as **reportable changes**.

Submission and acceptance of a reportable change to WHO should occur prior to the implementation of the change, i.e., the release of the changed prequalified/EUL-listed product into the market.

A reportable change can be categorized as having a potential Low or a High/Moderate Impact according to its nature and extent (see definition in point 1.4 above and how to determine the impact (see section 44 below).
The manufacturer takes responsibility for evaluating if the change is reportable and managing the risks associated with changes during its change management process, as well as, for appropriate reporting in the Reportable Change Request to WHO (categorized as High/Moderate Impact *vs.* Low Impact).

The Change Request Form (WHO document PQDx 119) and supporting documentation will be verified by WHO for accuracy of the risk categorization and completeness of the application (see section 6):

- **High/Moderate-impact reportable changes** will undergo a review of submitted data by the WHO. In case the manufacturing of changed product batches is required as part of the change control process (e.g., process validation pilot batches), changed batches should only be released to the market after the change is accepted by WHO.
- **Low-impact reportable changes** will be accepted by WHO upon checking the risk categorization of the submitted data and will not require a review of data before implementation.

Depending on the type of change, the assessment may also necessitate a site inspection(s) and/or a performance evaluation. Manufacturers are encouraged to consult with WHO in advance when planning to introduce a change that may require such activities.

All change-related activities will remain within the scope of post-prequalification periodic inspections or post-EUL reassessments.

3.3 Changes requiring a new prequalification or EUL application

In cases where a change results in a product or application information that substantially differ from what was originally accepted, a new prequalification or EUL application can be required.
In cases duly justified, WHO will notify the manufacturer that a new application is required. This application will undergo prequalification or EUL assessment, according to WHO applicable guidance.

The changes listed below are examples of changes that would require submission of a new application for prequalification/EUL:

- a change in what is detected (i.e., the biomarker, analyte or measurand);
- changes replacing antigens, antibodies, primers or solid phase;
- a change to the specific disorder, condition, or risk factor of interest that

it is intended to detect, measure or differentiate;
- a change replacing the test result format from a qualitative or quantitative or vice versa;
- a change in the biological or chemical principle of the test;
- a change in the design of test technology or test automation.

The combination of several changes that, in isolation, would not require submission of a new application could also result in the need for a new prequalification/EUL application, this would be determined on a case-by-case basis. Manufacturers should seek advice from WHO when planning to introduce several changes at the same time.

4 Determining the impact of a reportable change

Determining the impact of the change is an important step as it will guide the manufacturer on the type of documentation requested for the Reportable Change Request and inform WHO's decision on the level of review required.

The classification of the impact as Low or High/Moderate impact is based on the severity of the associated hazardous situation and risks, which includes, but is not limited to an assessment of the change potential impact on test functionality, performance, or safety:

- Changes to the design or composition of the IVD;
- Redevelopment including state-of-the-art product improvements;
- Changes to the critical components or products parts attributes or specifications;
- Changes to a manufacturing process, technologies, facilities, or equipment;
- Changes to the organization of the manufacturer or critical suppliers;
- Changes to the manufacturing, QC and release workflow;
- Changes to the intended use and /or test procedure;
- Changes introducing new safety or performance considerations necessitating new clinical and/or analytical studies;
- Changes that may affect regulatory approval in other jurisdictions, potentially influencing compliance with WHO prequalification or EUL specifications; and/or,
- Changes to materials or processes that influence environmental safety, including disposal requirements or compliance with hazardous material regulations;
- Changes to the product or accessories that would impact compliance with IMDRF Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices [4];

Consideration shall be given to the potential impact of the change implementation on the overall residual benefit/risk evaluation of the IVD as per **ISO 14971** [5]. This includes a determination of whether the change could:

- Introduce new hazardous situations that have not been previously addressed; or alternatively, may not introduce a new hazard but may require updated mitigation measures to prevent generating new hazards;
- Adversely affect the risk associated with existing hazards (risks re-evaluation);
- Alter the details of any of the information submitted for prequalification or EUL assessments (related to the dossier, manufacturing site(s) inspection, or performance evaluation), such as the intended use and/or compliance with the Essential Principles of safety and performance of medical devices and in vitro diagnostic products [4]; and/or, Affect the continued compliance of the QMS with the relevant standards.

When assessing the impact of a change, the manufacturer is not expected to create new documentation specifically for the WHO Reportable Change Request Application. Instead, the manufacturer should rely on its established internal procedures and the documentation already developed as part of its internal change management process. (See Figure 1. Flow diagram for initiating, categorizing and reporting a change.

The required set of information for the submission of Reportable Change Request Application, is detailed **in Appendix 1** depending on whether the change is classified as Moderate/High impact or Low Impact reportable change.

A list of examples of changes and their impact categorization is provided in **Appendix 1**. These are only examples, and each case must be assessed within its specific context. It remains the sole responsibility of the manufacturer to evaluate and categorize the impact of any changes accordingly.

If WHO disagrees with the assigned potential impact category of a change, the manufacturer will be notified during the risk categorization check (also see section 6):

- For changes reclassified as Low impact, approval may be granted without requiring a full assessment.
- For changes categorized as Medium/High impact, WHO will request additional information for full assessment, as necessary (see Figure 2 below).

5 Submitting a reportable change request

5.1 Reportable change request application

Reportable change must be submitted using a completed "*Change Request Form for WHO Prequalified and Emergency Use Listed In Vitro Diagnostics*" (WHO document PQDx 119) along with supporting documentation to WHO Prequalification Team – Diagnostics. The rationale for determining whether a change is reportable must be documented under the QMS change control process.

Submissions should be done **only electronically.** Please refer to the WHO PQ IVDs webpage

[https://extranet.who.int/prequal/vitro-diagnostics] for timelines and the latest instructions on how to proceed. The documents to be submitted are described in the *Change request form for WHO Prequalified and Emergency Use Listed In Vitro Diagnostics* (PQDx 119).

Change management relies on documented, controlled, and accepted processes to assess, plan, review, verify, validate, approve, and implement changes. Relevant change control processes shall be applied, and when applicable, design change documented, to ensure that outputs are still traceable to inputs after the change implementation. Documented evidence should establish data traceability and demonstrate proper risk mitigation and ongoing device's safety and performance. (See Figure 1. Flow diagram for initiating, categorizing and reporting a change.

WHO will not accept any changes without justification/rationale on their impact assessment and supporting documentation.

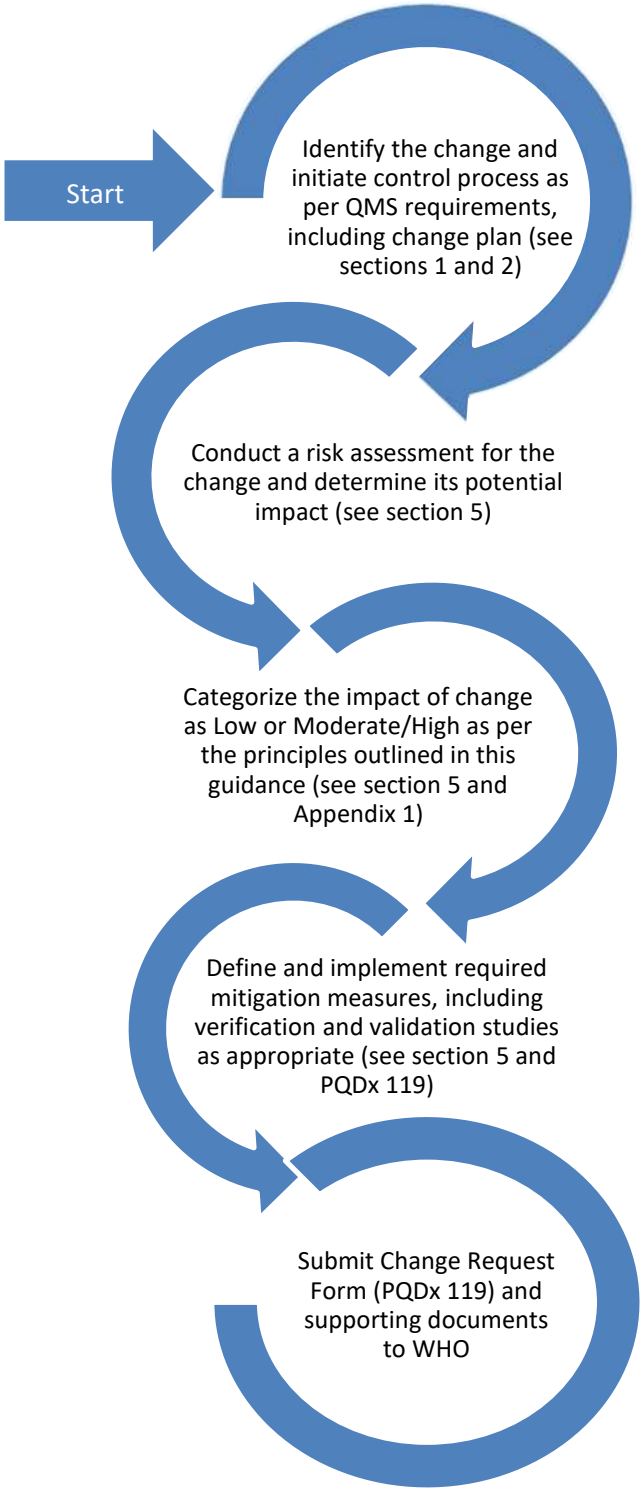

Figure 1. Flow diagram for initiating, categorizing and reporting a change.

5.1.1 Reportable administrative changes

For an administrative change that necessitates updating the WHOPAR without impacting the product's design or manufacturing process, the manufacturer must submit a completed "*Change request form for WHO Prequalified and Emergency Use Listed In Vitro Diagnostics (*PQDx 119*)"* along with any relevant information on the change, including:

- a declaration that the change only affects the product name, product code(s) and/or manufacturer name and has no impact on the quality, safety and/or performance, as supported in the submitted prequalification or EUL documentation, and the reason(s) for making the changes; and
- the new product labelling (i.e., labels, instructions for use, and any other printed or electronic labelling material) and the redlined version of the aforementioned.

5.2 Formatting requirements for submissions

- Electronic copies of the PQDx 119 and supporting documentation must be submitted as per the most up-to-date instructions provided by WHO. Searchable, unprotected PDF file format is preferred.
- The layout and order of this documentation must be easy to follow, and documents must be appropriately identified. Attachments to the Change Request Form must be clearly identified and divided into sections as indicated in the *Change request form for WHO Prequalified and Emergency Use Listed In Vitro Diagnostics* (PQDx 119).
- A separate cover letter is not required.
- File names should be as concise as possible, but descriptive of their content and meaningful to the assessors. File names can be up to 50 characters-long and can have spaces, dashes (not elongated dashes), underscores, and periods. However, the name of the file must not contain any of the following special characters or it will fail the loading process:

  - tilde (~)
  - vertical bar (|)
  - asterisk (*)
  - forward slash (/)
  - elongated dash (–)
  - backward slash (\)
  - apostrophe (')
  - greater than sign (>)
  - single quotation mark (‘)
  - less than sign (<)
  - double quotation marks (“)
  - question mark (?)
  - colon (:)
  - pound sign (#)
  - various other symbols (e.g., → ,*,β,α, ∞,±,™)

- When capturing data or creating a PDF from a source document (e.g., Microsoft Word document) using Adobe® plug-ins, please consider there is a risk that information may not display correctly because assessors may not have access to the required plug-ins.
- All PDF files should be created directly from the source documents whenever feasible rather than creating them by scanning. PDF documents produced by scanning paper documents are far inferior to those produced directly from the source document, such as a Microsoft Word document, and thus should be avoided if possible. Scanned documents,

particularly tables and graphs, are more difficult to read.

- For any scanned document, it is highly recommended that optical character recognition (OCR) is applied so that the text is searchable. Check that the content has been correctly converted by: (1) highlighting an area of text and (2) searching for a word or phrase. If the word or phrase is not returned in the search, then the OCR did not recognize the text.
- WHO recognizes that the use of OCR may not be feasible in some cases for documents with figures and images. Hence, there may be cases in which it is appropriate to include scanned documents in the electronic submission.
- Submit all documents presented in the Reportable Change Request in English (unless other arrangements have been made with WHO prior to submission of the documentation).
- Any translations of documents must be carried out by a certified translator. Provide an official document attesting to the accuracy of the translation and details on the credentials of the translator.
- Provide both the original and the translated documents.
- All measurement units used must be expressed in the International System of Units (SI).

Submissions not meeting the above formatting requirements will not be considered for assessment.

An overview of the Process for initiating, categorizing and reporting a change is presented in Figure 1.

6 Assessment of change request by WHO

6.1 Process for handling applications

Once WHO receives the completed Change Request Form PQDx 119 and supporting evidence, the completeness of the submission will be verified, as well as the correctness of the risk categorization, in order to determine the assessment pathway:

- Changes pertaining to technical aspects of the product are managed and overseen by the **WHO PQ IVD Assessment team.**
- The review of changes pertaining to QMS aspects are assessed by the **WHO PQ Inspection Services.**

An overview of the Reportable Change Request assessment process is presented in Figure 2.

If the provided documentation is complete:

- **Low impact changes** will be accepted by WHO upon the risk categorization check, and a full technical review, will not be conducted.
- **High/Moderate impact changes** will undergo a technical review as per the WHO document *Overview of the prequalification of in vitro diagnostics assessment* (PQDx 007).

If the submitted documentation is incomplete, the manufacturer will be notified and requested to provide the missing information within a timeframe specified by WHO. The manufacturer will

have up to two opportunities to submit the required additional information. If the documentation remains incomplete after these attempts, the application will be considered not ready and closed, the manufacturer will be then invited to submit a new application.

If WHO disagrees with the assigned potential impact category of a change, the manufacturer will be notified during the risk categorization check:

- For changes reclassified as Low impact change, approval will be granted without requiring a full assessment.
- For changes reclassified as Medium or High impact, WHO will request additional information.

As stated above, the manufacturer will have up to two opportunities to submit the required additional information. If the documentation remains incomplete after 3 rounds of review, the application will be closed, and the manufacturer will be invited to submit a new application. (see Figure 2.)

Any Change Requests, including those already accepted by WHO, may be followed up during post-prequalification monitoring activities (e.g., verification of records and related activities auditing during post-prequalification inspections).

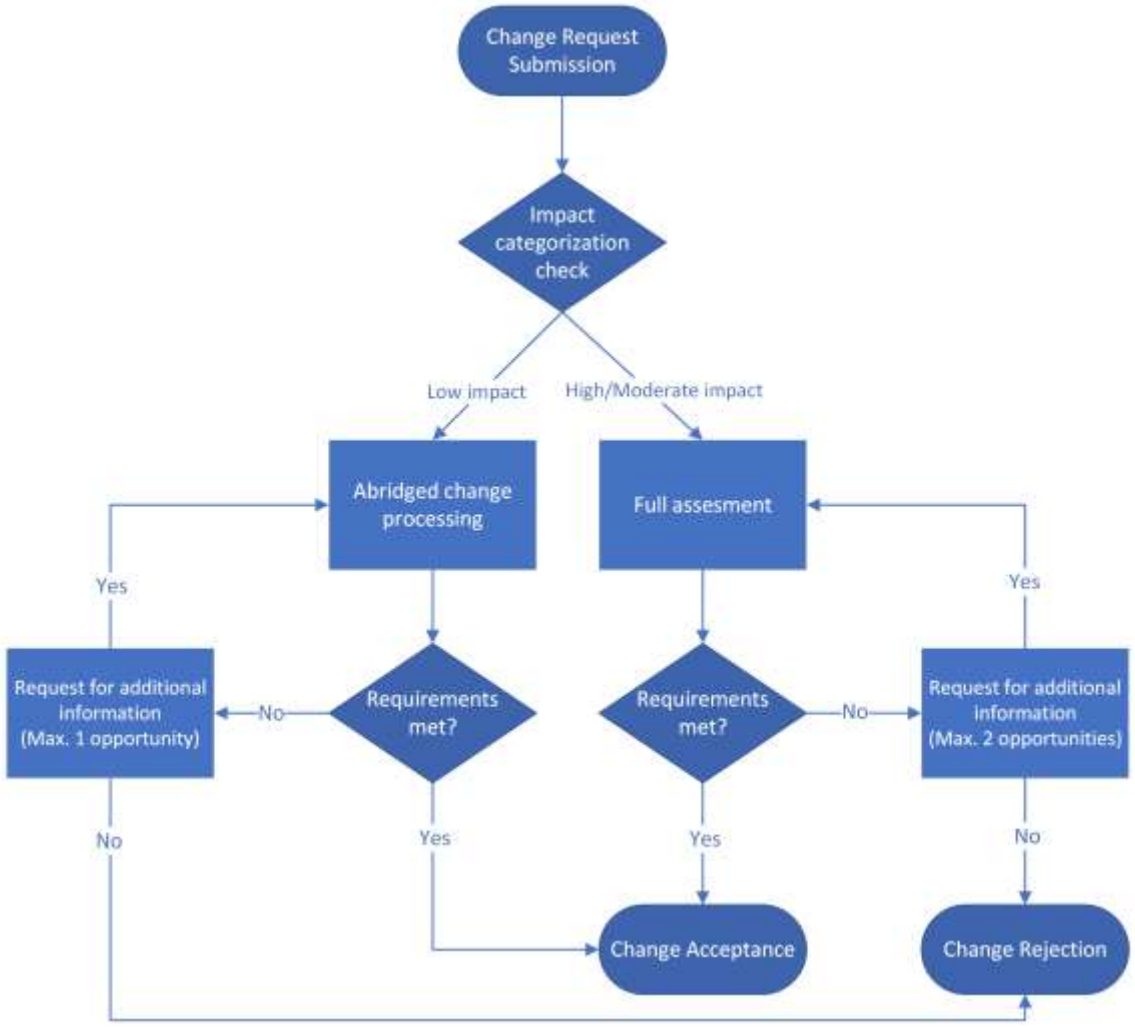

Figure 2. Overview of the change request assessment process.

6.2 Abridged assessment of high/moderate impact changes

If the manufacturer can provide objective evidence that the exact same proposed High/Moderate impact change has previously undergone stringent assessment and approval by a recognized National Regulatory Authority (NRA) as defined in the WHO document *Abridged prequalification assessment: prequalification of in vitro diagnostics* (PQDx_173), the change request may be accepted upon the risk categorization check. In this case, the same requirements as for a Low impact change would apply to the High/Moderate impact change submission requirements (see PQDx 119).

7 Outcome of assessment of the change request

Upon assessment of the application and supporting documentation, WHO will inform the

manufacturer of the outcome in writing.

The need to perform a manufacturing site(s) inspection and/or a laboratory evaluation will be determined based on the nature of the change and its potential impact on the quality, safety and/or performance.

Where a change is found acceptable, it will be notified to the manufacturer who may release the Prequalified or EUL listed product into the market.

As needed, WHO may update the public report and its lists of prequalified or EUL-listed IVDs to reflect the change. Information on the change may be included in the updated WHO prequalification or EUL public reports (WHOPAR and WHOPIR).

As outlined in Figure 2, if the application or submitted data are deemed incomplete, the manufacturer will be given two opportunities to resubmit additional information or evidence to address any deficiencies identified in the submitted documentation resulting in a maximum of 3 rounds of review.

If the submitted documentation supporting the change does not meet WHO prequalification requirements or the requested information is not provided by the manufacturer within the specified time, WHO will not accept the change and the application will be closed. In this case, the manufacturer may resubmit a new change request application, provided they have all the necessary elements or updated information.

8 Change reporting and failure to report

As described in this guidance document, reporting of changes is mandatory for all prequalified and EUL-listed IVDs. It is the manufacturer's responsibility to notify WHO of changes, as described in this guidance document, to keep the prequalification or EUL status of the IVD up to date (see section 7 above).

By failing to report such changes, manufacturers could compromise:

- Compliance with WHO requirements: Unapproved changes may result in the IVD no longer aligning with prequalification criteria.
- Procurement eligibility and market access: IVDs that do not comply with WHO Prequalification requirements risk being delisted from the List of WHO Prequalified IVD Products, making them ineligible for procurement by global health agencies.

As part of routine post-prequalification activities, WHO inspection services may review the compliance of the manufacturer processes to the requirements of this document.

Failure to submit reportable change in accordance with the requirements set in this document or non-fulfilment of one or more of these requirements could result in the assignment of nonconformity against the manufacturer's QMS and may lead to the publication of a Notice Of Concern or delisting of the IVD.

9 Change request assessment fees

The cost of the activities required to assess the change will be covered in part by the manufacturer. A non-refundable change request fee (please refer to WHO document *PQDx 299 Prequalification fees: WHO prequalification of in vitro diagnostics*) will contribute to the costs associated with change documentation review and dissemination of change information. The assessment of the change will commence upon fee payment.

WHO reserves the right to decide, based on the change assessment findings, whether an IVD meets this guidance's requirements. Therefore, payment of the change assessment fee does not guarantee that the change will be accepted. WHO also reserves the right to reject the proposed change(s) at any stage if the manufacturer is not able to, or fails to, provide the required information in a specified time, or when the information supplied is inadequate to effectively conduct the change assessment.

10 Relevant documents

- WHO. Overview of the prequalification of in vitro diagnostics assessment. PQDx_007. Geneva, Switzerland. World Health Organisation; 2021

- ISO 13485:2016. Medical devices – Quality management systems – Requirements for regulatory purposes. Geneva, Switzerland: International Organization for Standardization; 2016.

- ISO 14971:2019. Medical devices – Application of risk management to medical IVDs. International Organization for Standardization; Geneva, Switzerland: 2019.

- IMDRF/GRRP WG/N47 FINAL:2018 Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices. International Medical Devices Regulators Forum (IMDRF) Management Committee; 2018

- CLSI. Evaluation of Stability of *In Vitro* Medical Laboratory Test Reagents. 2nd ed. CLSI guideline EP25. Clinical and Laboratory Standards Institute; 2023.

- NB-MED/2.5.2/Rec2. Reporting of design changes and changes of the quality system. Co-ordination of Notified Bodies Medical devices (NB-MED) on Council Directives 90/385/EEC, 93/42/EEC and 98/79/EC; 2008

- FDA: Deciding When to Submit a 510(k) for a Change to an Existing Device. Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER), MD, USA; 2017

- FDA: Guidance for Industry and Food and Drug Administration Staff. 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75- Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes. Center for Devices and

Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER), MD, USA; 2019

- FDA: Guidance for Industry and Food and Drug Administration Staff. Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process. Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER), MD, USA; 2008

- FDA: Guidance for Industry and Food and Drug Administration Staff. Manufacturing Site Change Supplements: Content and Submission. Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER), MD, USA; 2018

- FDA: General Principles of Software Validation; Final Guidance for Industry and FDA Staff. Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER), MD, USA; USA; 2002

- FDA: PMA Supplements and Amendments | FDA Accessed 21 June 2024

- FDA: Real-Time Premarket Approval Application (PMA) Supplements. Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER), MD, USA; 2019

- MDCG 2022-6 - Guidance on significant changes regarding the transitional provision under Article 110(3) of the IVDR. Medical Device Coordination Group (MDCG), Directorate-General for Health and Food Safety, 2022

- Health Sciences Authority of Singapore. GN-21: Guidance on Change Notification for Registered Medical Devices. Revision 5. Singapore; 2023

- TGA: Varying entries in the ARTG: medical devices and IVDs. Therapeutic Goods Administration (TGA). ACT, Australia; 2023

- Health Canada: Guidance for the Interpretation of Significant Change of a Medical Device. Health Products and Food Branch, Ottawa, Ontario; 2011

11 Contact information

Any inquiries regarding changes to in vitro diagnostics should be addressed to: diagnostics@who.int

12 References

1. GHTF/SG1/N071:2012 Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'. Global Harmonization Task Force (GHTF) Steering Committee; 2012. Accessed 30 April 2025

2. ISO 13485:2016. Medical devices – Quality management systems – Requirements for regulatory purposes. Geneva, Switzerland: International Organization for Standardization; 2016.

3. World Health Organization. (2018). Risk management for manufacturers of in vitro diagnostic medical devices. World Health Organization. https://iris.who.int/handle/10665/274300. License: CC BY-NC-SA 3.0 IGO

4. IMDRF/GRRP WG/N47 FINAL:2018 Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices. International Medical Devices Regulators Forum (IMDRF) Management Committee; 2018. Accessed 30 April 2025

5. ISO 14971:2019. Medical devices – Application of risk management to medical IVDs. International Organization for Standardization; Geneva, Switzerland: 2019.

Annex 1: Examples of reportable change impacts

Non-exhaustive list

	Type of reportable change	Potential impact	
		Low	High/Moderate
	Design changes and changes to intended use		
1.	Change to the intended use, indications for use or conditions of use of the device.		X
2.	Change to test protocol such as specimen preparation, test procedure, reading time, workflow, incubation time, operational conditions, reagents, volumes, etc.		X
3.	Change to intended purpose, i.e., the manufacturer-defined automation process (including change to a new smaller/larger model if the IVD is an instrument) or the change from a manual procedure to an automated procedure for use.		X
4.	Change to the method principle, operating principle; including preanalytical conditions, analytical or interpretation methods.		X
5.	Change to the device or components in use and shelf-life storage conditions and time.		X
6.	Change to the function of the IVD (e.g., screening, monitoring, diagnosis or aid to diagnosis, staging or aid to staging of disease, prediction, self-testing).		X
7.	Change to the specific disorder, condition, or risk factor of interest that the IVD is intended to detect, define, or differentiate.		X
8.	Change in performance claims or design specifications.		X
9.	Change from qualitative to semi-quantitative or quantitative test results or vice versa.		X
10.	Addition of specimen type (e.g., serum, plasma, whole blood, oral fluid, sputum, urine, dried blood spots) or new anticoagulants for plasma specimens.		X
11.	Removal of a specimen type (e.g., serum, plasma, whole blood, oral fluid, sputum, urine, dried blood spots) or anticoagulants.	X	
12.	Change to the intended population including any new or extended use (e.g., addition of neonates, antenatal women).		X
13.	An addition of a contraindication, precaution, or	X	

	warning for the device.		
14.	A deletion of a contraindication, precaution, or warning for the device.		X
15.	Change in the stability data resulting in an extension of the claimed shipping, in use, and/or shelf-life stability of the IVD product.		X
16.	Change in the stability data resulting in a shortening of the claimed shipping, in use, and/or shelf-life stability of the IVD product.	X	
17.	Physical changes to the outer packaging (e.g., change of pack size).	X	
18.	Change to interpretation algorithm(s) or software or modification of the assay cut off that can impact the performance or safety characteristics or the intended purpose of the device.		X
19.	Change to quality control panel members' specifications for cut off control or release.		X
20.	Changes to biological materials (e.g., changes to the supplier; source, method of preparation, purification, etc.).		X
21.	Software change that impacts critical steps of the assay protocol and/or result interpretation.		X
	Changes in materials/components		
22.	Changes to the formulation of reagents in the assay that may result in a change of performance (either increase or decrease) such as: • Changes in the conjugate or substrates; • Changes in specimen preparation such as a nucleic acid extraction method; • Change of preservatives; • Changes from liquid to lyophilized reagents or vice versa; • Changes in ingredient concentration.		X
23.	Changes to reagents supplied with the IVD (e.g., quality control reagents, calibrators, buffer, etc.).		X
24.	Changes to accessory products supplied with the IVD (e.g., lancet; specimen transfer device).		X
25.	Changes to accessory components supplied with the IVD (other accessories, with no impact on the protocol or performance of the devices; etc.).	X	
26.	Changes to the test protocol of an IVD such as		X

	specimen pretreatment, incubation time, operating temperatures, calibration, etc.		
	Changes to the manufacturing process		
27.	Move/relocation of finished product manufacturing, assembling or other processing equipment from one location to a different location within the same site.	X	
28.	Move/relocation of finished product manufacturing, assembling or other processing equipment to a different site.		X
29.	Addition of new manufacturing lines applying the same technology, within the same site.	X	
30.	Inclusion of a new facility (manufacturing facility, warehouse, etc.)		X
31.	Move of manufacturing, processing or packaging from a supplier to the manufacturer's facility.		X
32.	Move of manufacturing, processing or packaging from the manufacturer's facility to a supplier or subcontractor.		X
33.	Relocation or introduction of a new warehouse.		X
34.	Change in the manufacturing process such as the introduction of new equipment for capacity increasing, change in workflow or manufacturing technology.		X
35.	Change to in process quality control method, reference material, specifications and/or protocols that reduces sampling or testing and/or relaxes acceptance criteria.		X
36.	Changes in Lot calibration/adjustment protocols and metrological traceability		X
	Changes to the QMS		
37.	Changes in the certification body, changes in the QMS certificates or change in the scope of certification.	X	
38.	Changes to the legal manufacturer including: • Change of ownership; • Change of legal entity status (e.g., Ltd, SA, etc.); • Changes in the name and/or address with no change in activities location.	X X X X	
39.	Changes to the lot release procedures, changes in the reference method, recognized standard, change in the responsibility, or change in the procedure for lot release by a third party or reference laboratory.	X	

	Change to the regulatory status		
40.	Change to the regulatory version of IVD.	X	X[2]
	Administrative or Labeling changes		
41.	Changes limited to the product name.	X	
42.	Changes limited to the product code(s) or catalogue number(s)	X	
43.	Changes limited to the manufacturer name/branding and/or legal entity structure.	X	
44.	Changes to the labelling and IFU of products that involve addition, removal and/or revision of warnings, precautions and/or contraindications arising due to safety and/or performance concerns.		X
45.	Changes in the IFU other than the ones originated from High/Moderate impact changes (e.g., administrative, revision for clarity, typos, etc.) that only requires update of the public report.	X	
46.	Addition of languages.	X	

WHO reserves the right to ask for additional documents during the review of the submission as needed.

[2] Changes to regulatory version of products prequalified under the abridged pathway are considered as to have a high potential impact.

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