



WHO PROCEDURE FOR CHANGES TO A WHO PREQUALIFIED IN VITRO DIAGNOSTIC

WHO Prequalification of In Vitro Diagnostics Programme

Table of Contents

1. Introduction	3
2. Intended Audience	3
3. Definitions	3
4. Abbreviations	3
5. Scope	4
6. Determining the significance of a change to a prequalified product	4
7. Change notification categories	5
7.1. Minor changes	6
7.2. Substantial changes	7
7.2.1. <i>Changes to manufacturing processes, facility or equipment</i>	7
7.2.2. <i>Changes to the manufacturing quality control procedures</i>	8
7.2.3. <i>Changes in design</i>	8
7.2.4. <i>Changes in product's software</i>	9
7.2.5. <i>Changes in materials/components</i>	10
7.2.6. <i>Changes to labelling</i>	10
7.3. Changes leading to a new product	11
8. Other changes requiring the submission of a Change Notification	11
8.1. Changes in product name, product code(s) and/or manufacturer name only	11
8.2. Changes in the regulatory or certification status of the product	11
9. Notification of changes to WHO	12
10. Change assessment fee	12
11. Attachments to the Change Notification form	12
12. Assessment of submitted Change Notification	13
13. Failure to comply with requirements to notify changes	14
14. Annual reporting of changes	15
15. Relevant documents	15
16. Contact information	16

1. Introduction

The World Health Organization (WHO) Prequalification of In Vitro Diagnostics (IVDs) Programme is coordinated through the department of Essential Medicines and Health Products (EMP). The aim of the WHO Prequalification of IVDs Programme is to promote and facilitate access to safe, appropriate and affordable IVDs of good quality in an equitable manner. Focus is placed on IVDs for priority diseases and their suitability for use in resource-limited settings.

The WHO Prequalification of IVDs Programme undertakes a comprehensive assessment of individual IVDs through a standardized procedure aimed at determining if the product meets WHO prequalification requirements. The prequalification assessment process includes three components:

- Review of a product dossier;
- laboratory evaluation of performance and operational characteristics; and
- manufacturing site(s) inspection.

Post-market surveillance is a WHO post-qualification activity which includes reactive and proactive measures, through complaint reporting and post-shipment/pre-distribution lot testing. Post-qualification also includes mandatory manufacturer notification of changes to the product or the quality management system.

2. Intended Audience

This document aims to provide manufacturers with information on changes to the product, to its regulatory or certification status and/or to the Quality Management System (QMS) that must be notified to WHO. It is recommended that manufacturers with WHO prequalified product(s) read this document.

3. Definitions

In vitro diagnostic ¹	A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for IVD, monitoring or compatibility purposes.
Manufacturer ²	Any natural or legal person with responsibility for design and/or manufacture of a IVD product with the intention of making the IVD product available for use, under his/her name; whether or not such a IVD product is designed and/or manufactured by that person himself/herself or on his/her behalf by another person(s).

4. Abbreviations

IVD	In vitro diagnostic
WHO	World Health Organization
QMS	Quality management system

¹ From Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

5. Scope

As part of the life cycle of a prequalified IVD, changes to it, its regulatory or certification status and/or the QMS under which it is produced may become necessary. Such changes (sometimes referred to as “variations”) to prequalified products may be minor, administrative or substantial. As part of their QMS, the manufacturer should have a system in place to design, validate and implement changes and to determine their significance.

This document describes the conditions under which WHO should be notified about changes to a prequalified product, its regulatory or certification status and/or to the QMS under which it is manufactured. Because it is not possible to describe all potential changes, this document provides guidance and a non-exhaustive list of generic examples. If in doubt or where the guidance does not sufficiently clarify a specific scenario, it is the manufacturer’s responsibility to seek advice from WHO and to properly document the reason why a change was not reported to WHO.

This document also describes when WHO considers a change to require a new application for prequalification.

Manufacturers should read this document carefully and notify changes to prequalified IVDs in accordance with the information provided in this document.

NOTE: The examples provided in this document are only illustrative and are not intended to be exhaustive.

6. Determining the significance of a change to a prequalified product

In order to meet the prequalification requirements, the manufacturer should establish, maintain and implement a procedure for categorizing and documenting any changes to the IVD, its regulatory or certification status and/or the QMS. The manufacturer should then assess the significance of any change, according to the guidance provided in this document.

To determine if a change requires notification to WHO, the manufacturer should evaluate the potential effect this change may have on the design, composition, safety, quality and/or performance of the IVD. Consideration should be given as to whether or not the change has influenced the risk profile of the IVD in any manner (for example, if it has introduced new hazards, eliminated existing hazards, or had any influence on the level of risk associated with a hazard). Such changes may require notification. Changes to the approved design, the construction, manufacturing site, raw material and/or composition of a prequalified IVD must be reported.

WHO recommends that the manufacturer’s decision on the type of change and the subsequent type of notification to WHO is based on the steps listed below:

- Identify the change and document the reasons for the change;
- conduct a risk analysis of the change and determine the potential impact of the change on the quality, safety and performance of the IVD (N.B. When an IVD is part of a system, and any individual characteristic of the IVD or system changes, the system as a whole should be evaluated);
- define the data needed to assess the impact of the change on the safety and performance of the IVD;
- review the risk assessment after necessary testing and before the introduction of hazard reduction steps (e.g. labelling including instructions for use); and

- categorize the change at this point.

Aspects that should be considered include whether or not:

- The change introduces new hazards that have not been previously addressed;
 - the change adversely affects the risk associated with existing hazards;
- the change alters the details in the application submitted for prequalification (related to dossier, inspection, or laboratory evaluation), such as the intended use and/or compliance with the Essential Principles³
- the change will introduce a different intended use (refer Section 5);
 - the performance data (analytical and clinical) for the original prequalified IVD are sufficient to demonstrate conformity of the changed product with the required characteristics and performance of the original prequalified IVD;
 - the change alters the manufacturing technologies or product range covered by the inspected QMS;
 - the change affects the approved design;
 - the change affects the continued compliance of the QMS with the relevant standards; and
 - the change affects the continued compliance with WHO prequalification requirements.

If the safety and/or performance of the product has been or will be affected by the change, this constitutes at a minimum, a substantial change.

If in doubt, the manufacturer should seek advice from WHO.

NOTE: Where several, simultaneous changes are being considered by the manufacturer, each change should be assessed separately, as well as the collective impact of the changes.

NOTE: Changes applied to an IVD must be undertaken in compliance with the requirements for control of design change as per ISO 13485:2003 “Medical devices -- Quality management systems - Requirements for regulatory purposes”

7. Change notification categories

After an IVD has been prequalified, the manufacturer must notify WHO regarding:

- any substantial changes to the IVD prior to implementation of the changes;
- any changes to the regulatory approval or certification status for the IVD, such as suspension or withdrawal of regulatory approval or certificate, in all countries of manufacture and supply; and/or
- any substantial changes to the QMS.

NOTE: Changes may only be implemented by the manufacturer after WHO has approved the request for change.

The requirement to notify a change is dependent on the significance of the change. Figure 1 provides an overview of actions required according to the classification of the change.

³ Please refer to the GHTF/SG1/N41R9:2005 Essential Principles of Safety and Performance of Medical Devices [Global Harmonization Task Force (GHTF) document; www.imdrf.org] for further information.

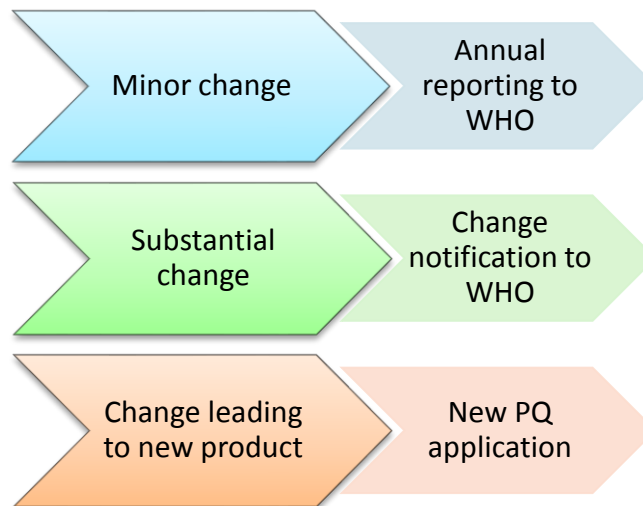


Figure 1 Product changes and required action by the manufacturer.

NOTE: The decision-making process to determine the type of change to the product (minor, substantial or leading to a new product) is the sole responsibility of the manufacturer.⁴

In the change notification, the manufacturer should provide a justification for having considered a change to be substantial.

7.1. Minor changes

A manufacturer may make a minor change to a product and/or to the QMS after prequalification without submitting a new application for prequalification or a Change Notification, **if the change does not affect the IVD's design, composition, safety and/or performance**. Such changes should be reported in the mandatory annual changes report to WHO.

Minor changes include, for example:

- Simple changes to the product documentation such as:
 - rewording or expanding for clarification;
 - translating from one language to another;
 - correcting typographical errors;
 - replacing (or complementing) written text by internationally recognized hazard symbols; and
 - moving component characteristics from a drawing note to a different document (e.g. Standard Operating Procedure).
- minor product changes that do not impact the safety and performance of the product (e.g. change in the colour of a label, provided it was not coloured originally to produce a warning)
- minor software changes that do not impact on the safety and performance of the product;

The manufacturer must always justify and document the decision to classify a change as minor.

7.2. Substantial changes

⁴ However, when determining the type of change to the product, it is recommended that manufacturers seek for advice from WHO.

A change that is demonstrated through the risk analysis to have an **impact on the IVD's design, composition, safety and/or performance** of a prequalified IVD, is considered a substantial change.

Substantial changes may:

- introduce a risk to the patient not previously identified;
- change the probability of existing hazards occurring; and/or
- alter the presentation of existing or new risks to the user (this can involve labelling changes or new indications for use).

Substantial changes include, but are not limited to, the types of changes listed below if they could reasonably be expected to affect the design, composition, safety and/or performance of the IVD:

- changes to manufacturing processes, facility or equipment;
- changes to the manufacturing quality control procedures;
- changes in design;
- changes to product's software;
- changes in materials/components;
- changes to labelling;
- changes to test procedure that require retraining and/or change in the Standard Operating Procedure or interpretation of test results; and
- changes to product performance specifications.

Substantial changes to a prequalified IVD require the submission of a Change Notification to the WHO Prequalification of IVDs Programme. The manufacturer must justify and document a decision to classify a change as substantial.

7.2.1. Changes to manufacturing processes, facility or equipment

A change to the prequalified manufacturing process, facility or equipment that could affect the IVD's design, composition, safety and/or performance is considered a substantial change and therefore requires a Change Notification to WHO.

Examples of such changes include:

- change or addition of a manufacturing site; and/or
- change in manufacturing process including introduction of new equipment.

For these changes, the manufacturer should submit:

- validation and verification studies including new equipment installation and qualification at the new site, and
- a summary of the new manufacturing process outlining the differences between the old and the new process.

A change in the manufacturer's name and/or address should be notified through a Change Notification and supplemented by:

- a QMS certificate for the new facility, if available;
- modified product labelling; and/or
- a manufacturer declaration of the manufacturing specifications in the new manufacturing facility.

NOTE: Change of the legal entity of the manufacturer will require a new application for prequalification.

When a supplier's manufacturing process, facility or equipment changes, this would not be a substantial change provided that the product specifications have not been changed and incoming inspections to evaluate the material/equipment provided by the supplier have not been changed.⁵

7.2.2. Changes to the manufacturing quality control procedures

Removal of test acceptance criteria, in-process inspections or final inspections without replacement of these activities are considered a substantial change. Likewise, changes to the manufacturing quality control procedures, such as the methods, tests or procedures used to control the quality of the materials or the product, are considered substantial if they alter the design specifications of the product.⁶ On the other hand, changing or adding new test acceptance criteria or test methods to provide equivalent or better assurances of reliability, as determined by the manufacturer, is not considered to be a substantial change.

If a substantial change also includes device design and/or labelling changes in addition to manufacturing changes, then the changes would automatically be considered so substantial that the product resulting from the change should be considered as a new product requiring submission of a new application for prequalification.

Changes to the manufacturing procedure or to the method of manufacture that, as a result of a risk analysis, are determined not to affect the safety and/or performance of a prequalified IVD, need not be submitted as Change Notifications.

7.2.3. Changes in design

Changes to design span the full spectrum from minor engineering changes to major changes in operating principles. All design changes must be evaluated, verified and validated according to the accepted procedures recorded in the QMS. The results of this process are then used to determine whether a change is to be categorized as minor, substantial or as a new product.

Almost all changes to control mechanisms of a product raise questions of safety and performance and therefore in most circumstances these changes are substantial. Changes to the design specifications, physical attributes, user interface, software or hardware may be substantial if they affect the indications, procedure or interpretations for use of the device.

The design change is likely to be substantial if the response to any of the following four questions is yes:

- Does the design change affect the intended use?
- Does the design change alter the test procedure?
- Are clinical data necessary to support the safety and performance of the changed product?
- Do the changes result in a change of the risk analysis, undertaken during the design verification and validation process, raise new issues of safety and performance, or change existing risks?

NOTE: The intended use of an IVD may include:

a) what is detected;

⁵ A change in the manufacturing process, facility or equipment must however undergo the appropriate validation.

⁶ See Section 5.3. for further information.

- b) the function of the product (e.g. screening, monitoring, IVD or aid to diagnosis, staging or aid to staging of disease);
- c) the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
- d) whether the product is automated or not;
- e) whether the test is qualitative or quantitative;
- f) the type of specimen(s) required (e.g. serum, plasma, whole blood, oral fluid, sputum, urine);
- g) the intended testing population (e.g. neonates, antenatal women).

In cases where the change consists only of tightening of design specifications within specified tolerances and where there is no creation of new features, the change is generally not considered to be substantial.

Changes that would typically be considered to be substantial include:

- A change to or addition of a specimen type (e.g. from serum to venous blood or plasma, or venous whole blood to capillary whole blood, or addition of oral fluid as a matrix);
- a change to the reagent volume or specimen volume required to perform the test;
- a change to the reading period (minimum or maximum);
- the addition of new anticoagulants for plasma specimens;
- a change to the automation process (e.g. a change to the throughput of an analyser);
- the addition of a new test kit quality control; and/or
- introduction of new reagents.

NOTE: Design change resulting in a new intended use should be considered as a new product.⁷ Manufacturers should contact WHO in order to determine if a new application for prequalification is required.

7.2.4. Changes in product's software

Many changes to a product's software will be considered substantial changes, for example:

- a software change, which impacts the control of the product, that may alter the reporting result of the diagnosis of a patient;
- a software change that modifies an algorithm impacting the test result;
- a software change that impacts the way data are read or interpreted by the user, such that the diagnosis of the patient may be altered when compared to the previous version of the software;
- a software change that replaces previously required user input/a closed loop decision;
- addition of a new feature to the software that may affect the diagnosis; and/or
- a software change that incorporates a change to the operating system on which the software runs.

If the software is modified to correct an error, for which there is a safety risk to the patient if the error is not corrected, this software change may be substantial. If software change is only intended to correct an inadvertent logic error that does not pose a safety risk and brings the system back into specification, this would usually not be a substantial change.

⁷ See Section 9 for further information.

The following would not be considered substantial changes:

- a software change that only relates to administrative functions, such as printing, faxing, improved image clarity, reporting format or additional language support;
- a software change that only modifies the appearance of the user interface with negligible risk of impacting the diagnosis; and/or
- a software change that disables a feature that does not interact with other features.

7.2.5. Changes in materials/components

Changes to raw materials/components used in the manufacturing process of an IVD often affect its performance characteristics, including sensitivity and specificity, and should be assessed as to their impact on the safety and performance of the IVD.

Changes to materials that necessitate testing of additional clinical specimens, or retesting of original specimens, to determine performance characteristics of the IVD, would be considered substantial, unless appropriate additional testing of clinical specimens confirms that the altered IVD still conforms to the performance specifications of the original prequalified IVD, as presented in the submitted product dossier, and no labelling changes are necessary.

Changes to the materials of an IVD that result in a change to the operating principle of the product are considered substantial.

Changes to materials that potentially affect the operating procedure of an IVD include changes in reaction components or materials such as calibration materials, or changes in methods such as specimen pre-treatment, incubation times and operating temperatures. If these changes result in altered performance characteristics that are reflected in the labelling (labels and/or instructions for use), then they are considered substantial.

Changes that would typically be considered to be substantial include:

- changes to the formulation of reagents in the assay that result in a change to the stability claims;
- changes in the antigen that do not change the intended use;
- changes in the conjugate or substrates that do not change the intended use;
- changes to the solid phase (e.g. change in nitrocellulose membrane) that would result in altered properties;
- changes in the sample preparation (e.g. the inclusion of a stabilizer to increase sample stability, incubation period or temperature);
- the addition of sodium azide or other agent as a preservative to a reagent of the test kit;
- changes to the source or processing of biological materials;
- changes from liquid to lyophilized reagents or vice versa;
- changes to the materials supplied with the IVD e.g. addition or deletion or change to collection device for finger stick blood collection.

7.2.6. Changes to labelling

Changes to a product, including changes to performance specifications and materials, often lead to labelling changes.

Changes to labelling to include additional languages are not considered substantial. **All other changes to the labelling, including labels and instructions for use, must be notified to WHO.**

7.3. Changes leading to a new product

Certain changes are of such magnitude that the result of the change should be considered as a new product. In general, WHO will consider a new IVD to be one where a change results in a product so different from the original version that the analytical and clinical data previously submitted for the original IVD no longer demonstrates a reasonable assurance of the safety and performance of the modified IVD.

In deciding whether to submit a Change Notification or to submit a new application for prequalification assessment for a modified IVD, the manufacturer should first ascertain if, and to what extent, one can rely on the analytical testing and clinical data submitted in the prequalification product dossier to support the safety and performance of the modified IVD. If both new analytical and clinical testing are needed to demonstrate reasonable assurance of safety and performance of the modified IVD, the manufacturer should assume that this constitutes a new IVD that requires a new application for prequalification.

For any of the changes listed below, the submission of a complete new application for prequalification is required:

A change:

- to what is detected, i.e. the analyte (measurand);
- to the function of the product (e.g. screening, monitoring, diagnosis or aid to diagnosis, staging or aid to staging of disease);
- to the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;
- to the automation status (e.g. non-automated to automated);
- on whether the test is qualitative or quantitative;
- of the intended testing population (e.g. neonates, antenatal women);
- to the antibody, antigen, nitrocellulose or microplate;
- of manufacturing site; and/or
- to the legal manufacturer.

Such changes leading to a new product, require a new application for prequalification.

8. Other changes requiring the submission of a Change Notification

8.1. Changes in product name, product code(s) and/or manufacturer name only

Changes in product name, product code(s) and/or manufacturer name only, must be notified to WHO. The manufacturer should submit a Change Notification form (PQDx_119) with the attachments listed below:

- a declaration that the change only affects the product name, product code(s) and/or manufacturer name and has no impact on the product design, composition, safety and/or performance, as supported in the submitted prequalification documentation and the reason(s) for making the changes; and
- the new product labelling (labels and instructions for use) reflecting the changes.

8.2. Changes in the regulatory or certification status of the product

Changes in the regulatory approval status for the product, such as suspension or withdrawal of regulatory approval, in any country of manufacture and supply, must be notified to WHO. The manufacturer should submit a Change Notification form (PQDx_119) with the attachments listed below:

- a description of the reasons for the change in the regulatory or certification status;
- any supporting documents from the relevant regulatory authority/certification body;
- new product labelling (labels and instructions for use) reflecting the changes, where applicable; and
- any other relevant information, such as reports on inspection findings.

9. Notification of changes to WHO

Minor changes to a prequalified IVD do not require the submission of a Change Notification to WHO. However, such changes must be reported through the annual reporting of all changes.

Substantial changes that could affect the design, composition, safety and/or performance of the IVD require the submission of a Change Notification to the WHO Prequalification of In Vitro Diagnostics Programme and in-depth assessment and approval by WHO is required prior to implementation of the change.

Any change that enhances the safety in the use of the IVD with no impact on performance may be placed into effect by the manufacturer prior to receipt of a written WHO approval, based on the change assessment, but after the manufacturer has received specific notification by WHO that the notified change can be placed into effect provided that:

- The Change Notification provides a full explanation of the basis for the changes;
- the Change Notification specifically identifies the date that such changes are being effected; and
- the change is made according to the change procedure in compliance with *ISO 13485:2003 medical devices: QMS*.

10. Change assessment fee

The cost of the activities required to assess the change will be covered in part by the manufacturer. The non-refundable change fee of 3,000 USD will contribute to the costs associated with change documentation review, manufacturing site(s) inspection, and dissemination of change information.

Changes in product name, product code(s) and/or manufacturer name only do not require payment of a change fee.

Manufacturers should note that WHO reserves the right to decide, based on the change assessment findings, whether a product meets the prequalification change requirements. Therefore, payment of the change assessment fee does not guarantee that the change will be approved. 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 period, or when the information supplied is inadequate to complete the change assessment effectively.

11. Attachments to the Change Notification form

The below attachments must be submitted with the Change Notification form:

1. A description of the product.
2. A detailed description of the planned changes as compared to the prequalified product (illustrative figures should also be included, where possible).
3. The reasons for the changes, including any information on adverse events or field failures that occurred in the original prequalified product.
4. A justification for having considered a change substantial.
5. A summary of the data supporting the change (a summary of key results), including:
 - 5.1. A summary of the procedures established for the identification, documentation, verification or validation, review, and approval of the changes.
 - 5.2. The statistical rationale for the sampling method used for the verification of the changed process.
 - 5.3. A description of how the manufacturing process that is intended to be changed will be monitored and controlled.
 - 5.4. A summary of the completed verification and/or validation studies that demonstrate that the manufacturing change can be made without significantly changing the safety and performance of the changed product. This should include:
 - 5.4.1. A description of the acceptance criteria.
 - 5.4.2. The test data analysis (including statistical methods).
 - 5.4.3. The statistical rationale for sample sizes.
 - 5.4.4. A list of deviations that occurred and detailed description of how each deviation was resolved.
 - 5.4.5. A determination of the impact of deviations on the final results.
 - 5.4.6. An explanation of how change control procedures were implemented, including the modifications of the manufacturing or quality control instructions or manufacturing specifications.
 - 5.5. A detailed risk assessment of the changes as related to safety and performance of the test.
6. The identification of the manufacturing site(s) where the changes will be implemented.
7. A summary of purchasing control procedures implemented to evaluate a new supplier or contractor, if the manufacturing change involves changes in suppliers of components or raw materials that are critical to the product performance or the use of a new contractor for a manufacturing process or quality control testing.
8. If applicable, the amended instructions for use with the changes highlighted.
9. Any action planned to inform the end user about the changes in the product (instructions for use, retraining, etc.).
10. A plan for follow up of the changed product (post market surveillance, end user feedback, etc.).
11. Any other relevant data supporting the change.

12. Assessment of submitted Change Notification

Once the Change Notification has been received by WHO, it will be reviewed to determine the actions required prior to the change approval.

The notification will be screened for completeness by WHO staff. This screening does not take into consideration the technical appropriateness of all the information provided within the documentation submitted. If the provided documentation is incomplete, the manufacturer will be informed and requested to provide supplements within a specified time period. There will be two opportunities to submit the required supplemental information before the change is rejected. The process will be terminated and the change rejected if the change notification does not contain all the required information, or where the submission timelines set by WHO are not met.

Once the change notification is determined to be ready for review, a non-refundable change fee of 3,000 USD will be levied.

WHO will perform a review of the submitted documentation and/or a manufacturing site(s) inspection in order to assess the change. The change documentation review and/or manufacturing site(s) inspection will be performed as per the Overview of the prequalification of in vitro diagnostics assessment document (PQDx_007).

The information submitted in the Change Notification will be reviewed and assessed by external experts (assessors) appointed by WHO. Assessors must have the qualifications and expertise in the relevant fields and must comply with the confidentiality and conflict of interest rules of WHO. Based on the review, WHO will inform the manufacturer if the change requires a manufacturing site inspection.

Any deficiencies in the submitted documentation and/or data identified in the change notification review will be communicated in writing to the manufacturer. The manufacturer will have the opportunity to submit one amendment to the original change notification.

The need to perform a manufacturing site(s) inspection will be established based on the nature of the change and its potential impact on the product composition, design, safety and/or performance.

Once WHO is satisfied that the change assessment of a product is complete and the overall findings demonstrate that the product meets all WHO prequalification requirements, the WHO list of prequalified products shall be updated to reflect the respective change. Information on the change may be included in the WHO prequalification public report.

If the change notification does not meet WHO prequalification requirements or where the requested information is not provided by the manufacturer within a specified time period, WHO may reject the change.

For changes accepted by WHO, the manufacturer may proceed to implement the proposed changes to the prequalified product.

13. Failure to comply with requirements to notify changes

WHO re-inspections will include a review of the compliance of the manufacturer to the requirements of this document. Failure to comply may result in delisting from the WHO list of prequalified IVDs.

14. Annual reporting of changes

Manufacturers must submit, for all prequalified products, annual reports listing all changes implemented during the calendar year. These will include minor and substantial changes, administrative changes and any other changes implemented by the manufacturer.

The annual report, in the format prescribed by WHO, must be submitted every year following prequalification. **The report should be submitted no later than by 28 February for the previous calendar year.**

WHO will review the list of changes implemented by the manufacturer. The manufacturer may be requested to submit additional information supporting any of the notified changes. If the information supplied by the manufacturer is inadequate or where the requested information is not provided by the manufacturer within a specified time period, the product may be removed from the list of prequalified IVDs.

The below information should be submitted for each implemented change:

- A detailed description of the change as compared to the prequalified product (illustrative figures should also be included, where possible);
- The reasons for the change, including any information on adverse events or field failures that occurred in the original prequalified product;
- Change classification (minor, substantial, administrative etc.); and/or
- A justification for having considered a change minor/substantial.

15. Relevant documents

- Overview of the prequalification of in vitro diagnostics assessment: Document PQDx_007
- ISO 13485:2003 *Medical devices - Quality management systems - Requirements for regulatory purposes* [International Organization for Standardization (ISO) document; www.iso.org]
- ISO 14971:2007 *Medical devices - Application of risk management to medical devices*
- GHTF/SG1/N41R9:2005 *Essential Principles of Safety and Performance of Medical Devices* [Global Harmonization Task Force (GHTF) document; www.imdrf.org]
- CLSI EP25-A *Evaluation of Stability of In Vitro IVD Reagents*; Approved Guideline (2009)
- U.S. Food and Drug Administration *Medical devices PMA Supplements and Amendments*
- U.S. Food and Drug Administration *real-Time Premarket Approval Application (PMA) Supplements* (2006)
- U.S. Food and Drug Administration *30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing method or Process Changes* (2011)
- U.S. Food and Drug Administration *Modifications to devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (2008)
- NB-MED/2.5.2/Rec2 *Co-ordination of Notified Bodies Medical devices (NB-MED) on Council Directives 90/385/EEC, 93/42/EEC and 98/79/EC: Reporting of design changes and changes to the quality system* (2000)
- Health Canada *Guidance document for the interpretation of substantial change* (2011)
- Health Sciences Authority of Singapore *Medical device Guidance GN-21: Guidance on change notification for registered medical devices* (2011)
- Therapeutic Goods Administration *Changes or variations to therapeutic devices in the ARTG* (1998)

16. Contact information

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